# sleep in Parkinson's disease

## a focus on nocturnal movements

Maartje Louter

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# Sleep in Parkinson's disease

## a focus on nocturnal movements

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*“Sleep is not just an unconscious state of mind“*

*–Unknown*

# Contents

# General introduction and outline of the thesis

## Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative disorder. Most symptoms and signs can be ascribed to a dopamine deficiency, resulting from progressive neuronal loss in the substantia nigra. Particularly later in the course of the disease, additional non-dopaminergic lesions arise that can also contribute to the symptoms. The estimated prevalence is 0.5–1% above the age of 60 years and more than 4% above 80 years. In the Netherlands, approximately 5.000 people are newly diagnosed with PD every year.[1] The diagnosis is made based on the UK Brain Bank Criteria which demand the presence of bradykinesia with either rigidity, tremor or postural instability (Box 1).[2] Although motor symptoms play a key role in diagnosing the disease, it is becoming increasingly clear that PD is not only a movement disorder. The involvement of noradrenergic, serotonergic, cholinergic and other neurotransmitter systems leads to the presence of a broad spectrum of non-motor symptoms in PD. In many cases these symptoms can even precede the appearance of motor symptoms.[3–10] A wide variety of non-motor symptoms can be present, such as autonomic dysfunction, cognitive problems, mood disorders and sleep problems.[4,6–8] The last decades it has become evident that the impact of these non-motor symptoms is a major determinant of the patient's quality of life, even more so than the motor problems.[11–13] Therefore, timely recognition and adequate treatment of these problems is very important for patients with PD. This thesis focuses on one specific non-motor feature that is both common and disabling for affected patients: disorders of sleep.

**Box 1.** Motor symptoms of Parkinson's disease

**Akinesia**
(slowness of initiation of voluntary movements or poverty of movements and movements that are smaller than attended)

*Accompanied with at least one of the following signs:*

**Muscle rigidity**
(increased muscle tone that can be felt during passive movement)

**4–6 Hz rest tremor**

**Postural instability**

# Sleep

## Normal sleep

Sleep is a universal phenomenon across species. Sleep is important for normal functioning during the day. During sleep the body relaxes and certain experiences of the day are stored as memory. Reduced hours of sleep or bad sleep quality result in fatigue during the day, but can also lead to an increased risk of cardiovascular problems.[14,15] Sleep can be measured with polysomnography (PSG), which is a combination of brain activity (electroencephalography, EEG), muscle activity (electromyography, EMG), eye movements (electrooculography, EOG) and associated cardiorespiratory parameters.[16] The sleep cycle can be divided in 4 stages. Stage 1, 2 and 3 are non-rapid eye movement (non- REM) sleep, the last stage is REM sleep. Box 2 shows the different sleep stages and their characteristics measured with PSG.[16] During one night several subsequent cycles of stage 1, stage 2, stage 3 and REM sleep are present. During the first cycles stage 3 sleep is more pronounced, at the end of the night REM sleep is more prominent (Figure 1).[16]

The amount of sleep a person needs is individually different. In general, optimal sleep duration is somewhere between 5 and 10 hours per night. Sleep structure changes over a persons' life. In a newly born child, during the first couple of months the distribution between wake, non-REM sleep and REM sleep is almost equal. Moreover sleep is spread over 24 hours. During childhood sleep consolidates in the nocturnal period. With increasing age the amount of wake increases and the amount of REM sleep decreases. Elderly subjects have more fragmented sleep.[17,18]

## Abnormal sleep

Having a bad night of sleep once in a while is, although troublesome, not uncommon. Several bad nights in a row, however, could indicate a sleep disorder. Disrupted night time sleep can cause daytime sleepiness and fatigue and therefore influence daytime functioning.[14,15] Sleep can be disrupted by many external factors such as noise, stress and pain. Sleep disorders caused by pathophysiological processes can also be present. Sleep problems may have a substantial influence on quality of life, sometimes leading to a diminished participation in social events or absence from work.[15]

Sleep disorders are classified according to the International Classification of Sleep Disorders, of which a second edition was published in 2005 and a third edition has recently been made available.[19] Box 3 describes the most common types of sleep disorders with some examples.







**Box 2.** Different sleep stages and their characteristics

**PSG and clinical characteristics**

**Non-REM sleep**

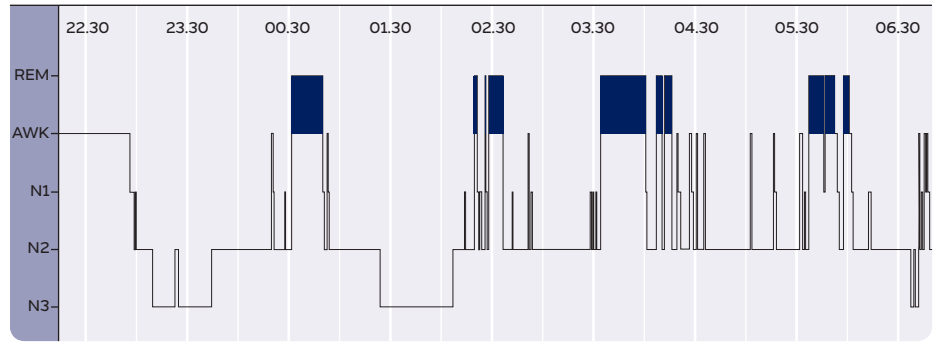
*Stage 1*
- EEG: alpha rhythm of wake drops out. A more slow end mixed pattern of amplitudes appears
- The muscles are active and the eyes roll slowly

*Stage 2*
- EEG: theta rhythm; with incidence of sleep spindles and K-complexes
- No eye movements, muscle tone is preserved

*Stage 3 (slow wave sleep)*
- EEG: delta activity, high amplitude waves at less than 3.5 Hz
- Sleeper is less responsive to the environment

**REM sleep (dream sleep)**
- EEG: mixed frequency EEG similar to stage 1 with saw tooth waves
- Chin EMG tone very low compared to tone in other sleep stages
- Rapid eye movements

**Figure 1.** Typical hypnogram of a healthy subject



# Sleep in Parkinson's disease

Already in 1817 James Parkinson wrote about sleep in his classic "An essay on the shaking palsy". Describing the patients he used phrases like "in this stage, the sleep becomes much disturbed", "but even when exhausted nature seizes a small portion of sleep" and "the trembling would increase until it awakened him: when he always was in a state of agitation and alarm".[20] In the years following this essay, sleep as a PD-related problem was underexposed, in fact like any of the other non-motor symptoms. In the last decades, however, the role of sleep problems as an important problem in PD has been increasingly recognized. Up to 90% of PD patients complain of having sleep problems.[21–24] In PD, sleep can be disrupted by a wide variety of causes. All "generic" sleep disorders can be present in PD patients, and some are particularly prevalent in this population.

## Nocturnal motor symptoms in PD

Although sleep disorders are considered to be among the non-motor symptoms in PD, the motor symptoms of the disease itself can also cause disrupted sleep. In clinical practice it is assumed that the motor symptoms of PD have a negative influence on sleep quality. Although tremor usually diminishes in stage 1 sleep, if persistent it could prevent a person from falling asleep.[22] Nocturnal hypokinesia could lead to difficulties turning around in bed which could cause sleep initiation or sleep maintenance problems.[25–28] The precise mechanism behind this impaired bed mobility in PD is not clear. The complaint is often referred to as "nocturnal hypokinesia", but rigidity, pain and overall muscle weakness could also be a part of the problem.[29,30] In clinical practice if a patient complains of having difficulty turning around in bed, nocturnal dopaminergic treatment is often started. However, scientific proof whether there is an actual relation between complaints of impaired mobility, number of body position changes and sleep quality is lacking. Previous studies have suggested that impaired bed mobility negatively influences sleep quality. PD patients were compared with healthy controls, showing that in a cohort with sleep maintenance problems, subjective presence of turning problems were more frequent in the PD group.[27] This suggest that difficulty turning interferes with sleep. However, these results could also be explained by a co-occurrence of both insomnia and impaired bed mobility in PD, without a causal relation. Other studies report increased nocturnal activity levels in PD patients compared to controls.[24,31,32] Possible explanations for this are sleep fragmentation leading to more wake or presence of specific nocturnal motor disorders such as REM sleep behavior disorder.





**Box 3.** Different types of sleep disorders

### Types of sleep disorders

**Insomnia**

*(problems initiating or maintaining sleep)*

- Adjustment insomnia
- Psychophysiological insomnia
- Inadequate sleep behavior

**Sleep related breathing disorders**

- Obstructive sleep apnea syndrome
- Central sleep apnea syndrome

**Hypersomnias**

*(excessive daytime sleepiness)*

- Idiopathic hypersomnia
- Narcolepsy

**Circadian rhythm disorders**

*(sleep disorders affecting the biological clock)*

- Delayed sleep phase disorder
- Advanced sleep phase disorder
- Jet lag disorder

**Parasomnias**

**(***abnormal movements during sleep)*

- Confusional arousals
- Sleep walking
- REM sleep behavior disorder

**Sleep related movement disorders**

*(abnormal movements during sleep)*

- Restless legs syndrome
- Periodic limb movement disorder

Whether subjective problems of having difficulty turning around in bed indeed lead to a decreased number of nocturnal movements has not been proven yet. Furthermore the influence of subjective and objective impaired bed mobility is not known. For clinical practice, however, an answer to these questions is important, especially in the choice of treatment.

In this thesis we addressed this underexposed part of sleep in PD. By studying both the subjective complaints as well as the objective signs of nocturnal movements and their influence on sleep parameters we addressed most of these questions. Furthermore, we studied if possible changes in nocturnal movement could serve as a pre-clinical marker in the early detection of PD.







## Outline of this thesis

Chapter 2.1 contains a detailed and comprehensive introduction about the latest developments in the recognition and diagnosis of the different sleep disorders that can be present in PD. We developed a structured, easy-to-use flow chart which can be used by every movement disorder specialist as an aid in the clinical detection of sleep problems in these patients. Furthermore we make suggestions with regard to the additional tests that can be done as part of the diagnostic trajectory, and offer recommendations when a patient should be referred to a sleep medicine center.

Although sleep disorders receive increasing attention in both clinical practice and in science, the actual importance of sleep disorders compared to other PD-related complaints is underexposed. Are sleep problems a reason to search for medical attention? In Chapter 2.2 we address this question. By using a subjective priority list we put sleep disorders into perspective with other symptoms and daily limits in PD. We studied a cohort of consecutive PD patients who were referred for problems other than sleep to our tertiary referral center. Prior to their visit, patients ranked their individual clinical priorities, indicating the most problematic domains for which they preferably requested medical attention. In addition we studied if presence of a sleep problem was a reason to put sleep on the priority list.

The second half of the thesis focuses on nocturnal movements in PD.

Chapter 3 deals with difficulties in movement during the night. As suggested, complaints of having difficulty turning around in bed could theoretically lead to bad sleep quality. This hypothesis was first tested in Chapter 3.1 by using sleep questionnaires. We studied the association between subjective complaints of impaired bed mobility in PD patients and sleep quality. Therefore we compared subjective sleep quality in PD patients with and without impaired bed mobility. Second, in Chapter 3.2 we studied whether subjective complaints of impaired bed mobility indeed lead to a decreased number of nocturnal movements. We objectified the complaint by measuring actual body position changes in both PD patients with and without impaired bed mobility. Furthermore we studied the influences of both the presence of subjective impaired bed mobility and the actual number of body positions changes on objective sleep parameters such as sleep efficiency and total sleep time.

Chapter 4 covers nocturnal movements in the pre-motor phase of PD. Nocturnal hypokinesia could lead to a decrease in axial movements during the night. Next to

a reduced number of turns, we also expected that patterns of the axial turns (e.g. speed and size of the body rotations) could be different. The pattern of nocturnal axial movements has not been studied before. Knowing that changes in pattern of nocturnal movements are present in patients with clinically overt PD, we were also interested to determine if these nocturnal differences could also be present before the actual diurnal motor symptoms develop. As such they could potentially be a pre-clinical marker for the development of PD. We hypothesized that PD patients would show different nocturnal movement patterns compared to healthy controls, and that smaller but still detectable differences in nocturnal movements would occur already in non-PD individuals with a potential high risk for future development of the disease.

In **Chapter 5** we addressed another sleep-related movement disorder known to precede PD by several years; REM sleep behavior disorder (RBD). The diagnosis officially requires a clinical interview and video polysomnography (v-PSG). In clinical practice, however, this is not always feasible, since it is time consuming and expensive. Therefore, there is a need for less expensive, easy to use devices to diagnose RBD. In a previous study actigraphy was suggested as a possible tool.[33] Specifically, the results in this latter study showed a significant increase in bouts classified as "wake" in PD patients with RBD. The study population however was small and diagnosis of RBD was not confirmed with v-PSG. In **Chapter 5** we therefore addressed this issue in more detail, by comparing a larger group of PD patients with and without RBD based on the gold standard. Furthermore we searched for an optimal cut-off point to actually implement the use of actigraphy in clinical practice.

**Chapter 6** summarizes the findings of this thesis and discusses these results. Finally, future challenges are being addressed.







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# Sleep
## and sleep disorders in Parkinson’s disease

# 2.1

# Recognition and diagnosis of sleep disorders in Parkinson’s disease

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Recognition and diagnosis of sleep disorders in Parkinson’s disease.

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## Abstract

*Sleep disturbances are among the most frequent and incapacitating non-motor symptoms of Parkinson's disease (PD), and are increasingly recognized as an important determinant of impaired quality of life. Here we review several recent developments regarding the recognition and diagnosis of sleep disorders in PD. In addition, we provide a practical and easily applicable approach to the diagnostic process, as a basis for tailored therapeutic interventions. This includes a stepwise scheme that guides the clinical interview and subsequent ancillary investigations. In this scheme, the various possible sleep disorders are arranged not in order of prevalence, but in a "differential diagnostic" order. We also provide recommendations for the use of sleep registrations such as polysomnography. Furthermore, we point out when a sleep specialist could be consulted to provide additional diagnostic and therapeutic input. This structured approach facilitates early detection of sleep disturbances in PD, so treatment can be initiated promptly.*








## Introduction

Sleep disorders are among the most common non-motor symptoms in Parkinson's disease (PD), with an estimated prevalence of 65% to more than 95%.[1–4] Sleep disorders negatively affect the quality of life.[5–7] Fortunately, specific treatment options are available, but adequate treatment requires a precise and timely diagnosis of the specific sleep disorder at hand. This recognition and diagnosis remains challenging in everyday clinical practice, because of the wide variety and intricate combinations of sleep disorders in PD.

The whole gamut of sleep disorders may occur in PD, including excessive daytime sleepiness, insomnia, nocturnal motor symptoms and sleep-related breathing disorders. Three main groups of causes can be identified. Sleep problems can be a primary disease symptom, caused by neuronal degeneration in sleep-regulating brain regions. An example is EDS in cognitive declined patients.[8] Second, sleep may be disrupted by other symptoms of PD, such as nocturnal motor symptoms (e.g. difficulty turning in bed) or autonomic dysfunction (e.g. nocturia). And third, many drugs used in the treatment of PD can affect sleep.[1,9–12] For example, selegiline –which is metabolized to methamphetamine and amphetamine– may cause insomnia.[13]

Most sleep disturbances can be diagnosed and treated by the movement disorders specialist. However, the diversity and complex origin of sleep disorders in PD may complicate the diagnostic trajectory. Ancillary investigations are needed occasionally, including polysomnographic recordings. In specific cases, the diagnostic and therapeutic help of a sleep medicine specialist can be useful.

To adequately treat sleep disorders in PD, an accurate diagnosis is crucial. Treatment options are diverse and depend on the specific sleep disorder(s) that are present. In Table 1, some of the most common sleep disorders are highlighted, together with specifically tailored treatment options. For more elaborate details on the treatment of sleep disorders in PD, we refer to previously published reviews.[14,15]

The purpose of this paper is twofold. We highlight the most important recent developments that have clinical relevance for the (differential) diagnosis of sleep disorders in PD. In addition – and based on this new knowledge – we provide a practical, easily applicable approach to the recognition and diagnosis of sleep disorders in PD and atypical parkinsonian syndromes.

Table 1. Therapeutic options of the most common sleep disorders in PD

| | | |
|---|---|---|
| Excessive daytime sleepiness | Disrupted nocturnal sleep | · Improve nocturnal sleep |
| | Medication side effect | · If possible discontinue or change medication |
| | Primary hypersomnia | · Stimulant medication<br>· modafinil[16]<br>· methylphenidate (no controlled studies) |
| Nocturnal motor symptoms | Nocturnal "off" | · slow release levodopa preparation[17]<br>· continuous dopaminergic stimulation (apomorfine, rotigotine, duodopa)[18,19] |
| | Restless legs syndrome<br>Periodic limb movement disorder | · increase nighttime dose of dopaminergic medication[20]<br>· opiate[20]<br>· gabapentin[20] |
| | REM sleep behavior disorder | · clonazepam[21]<br>· melatonin[22] |
| Sleep related breathing disorders | Obstructive sleep apnea | · continuous positive airway pressure[14] |
| | Nocturnal stridor | · continuous positive airway pressure[23–25]<br>· tracheotomy[26] |

## Sleep diagnostics

### The sleep history

The clinical interview remains the single most important diagnostic instrument. Although sleep disorders are common in PD, they are not always mentioned spontaneously by the patient, as was recently shown.[27] A few quick screening questions, probing both nocturnal sleep and daytime sleepiness (see Table 2), should be asked on a regular basis in every PD patient. When these questions raise suspicion of a relevant sleep disorder, a structured history is the essential starting point of the diagnostic trajectory. Table 2 describes the various topics that should be covered in such a comprehensive sleep history.







Table 2. Key elements of the sleep history for PD patients

**Screening questions**

- sleep onset insomnia (sleep latency > 30 minutes)
- frequent awakenings
- non-restorative sleep (unrefreshed in the morning, tiredness/sleepiness just after awakening)
- daytime sleepiness (either unwanted sleep episodes or napping)

**When a sleep disorder is suspected**

- check habitual bedtimes, sleep latency, number and duration of awakenings, total sleep time
- screening for nocturnal motor symptoms including "off" symptoms and RBD
- screening for nocturia, nocturnal pain
- screening for sleep related breathing disorders
- screening for mood and anxiety disorders, hallucinations
- daytime sleepiness: frequency, warning signs, driving
- detailed medication schedule, relation to sleep symptoms

**Further questioning:**

Sleep relating breathing disorders
- snoring, witnessed apneas, nocturnal stridor, daytime stridor
- nocturia, night sweats, dry mouth in the morning, morning headaches

REM Sleep Behavior Disorder
- sleep talking, shouting, swearing
- gross body movements resembling "dream enactment" (often aggressive)

Restless Legs Syndrome
- check diagnostic criteria (see Table 3)

Nocturia
- frequency, volume, urologic symptoms during the day
- fluid intake in the evening, caffeine and alcohol use, medication such as diuretics

Primary insomnia
- circumstances around onset, sleep hygiene, extending bed times "to try and catch some sleep"
- worrying when lying awake, frequently checking the clock
- mood and other co-morbid disorders

Excessive daytime sleepiness
- frequency and duration of unintentional sleep episodes
- circumstances, warning signs, relation with dopaminergic medication
- driving, effect of planned naps

## Sleep questionnaires

Sleep questionnaires can help to collect data in a standard fashion, although they are no substitute for a personal clinical interview. In the past years, several sleep questionnaires have been developed to identify sleep disorders in PD. A recent study of The Sleep Scale Task Force reviewed these scales and made recommendations for their use.[28] The Pittsburgh Sleep Quality Index (PSQI) is a well-validated measure of nocturnal sleep quality and severity of nighttime sleep disturbances.[29] The Parkinson's Disease Sleep Scale (PDSS) is a more general scale which specifically rates sleep problems in PD.[30] The Epworth Sleepiness Scale (ESS) is recommended to screen for excessive daytime sleepiness and to rate its severity.[31] A specific screening for sleep attacks is provided by The Inappropriate Sleep Composite Score (ISCS).[32] Nighttime sleep problems and excessive daytime sleepiness are both part of the Scales for Outcomes in Parkinson's Disease SLEEP (SCOPA-SLEEP), but this scale has not yet been validated against other – objective – sleep measures.[33]

The Sleep Scale Task Force has also commented on the fact that many available sleep questionnaires offer an overall rating of the severity of night- or daytime sleep problems, but are not intended to diagnose a specific sleep disorder. Recently, the PDSS has been revised and updated to tackle this issue. The PDSS-2 now screens for sleep disorders that are common in PD, such as restless syndrome, nocturnal hypokinesia and/or pain and sleep apnea.[34] The PDSS-2 was validated using a semi-structured interview, but a validation against objective measurements such as polysomnography has not yet been performed.

## Sleep registrations

A number of neurophysiological studies allow for the assessment of sleep architecture and the detection of nocturnal sleep disorders as well as excessive daytime sleepiness, but these sleep registrations should always be interpreted carefully and in combination with the clinical interview. The mainstay technique is polysomnography (PSG): the simultaneous recording of multiple signals to measure both sleep itself and associated physiological parameters such as breathing. Additional audiovisual recording can be very useful, especially for diagnosing nocturnal movement disorders, such as REM sleep behavior disorder. Excessive daytime sleepiness can be objectified using the Multiple Sleep Latency Test (MSLT). Poryazova et al. found a significant correlation between ESS scores >10 (indicating excessive daytime sleepiness) and short mean sleep latency (≤5 min) as measured with the MSLT.[35] Although in daily practice the clinical interview and additional questionnaires are often sufficient to diagnose excessive daytime sleepiness, an MSLT can be considered when







an objective diagnosis is needed (e.g. in relation to driving) or when there is difficulty separating sleepiness from related complaints of fatigue.

## Diagnostic strategy

Most reviews on sleep disorders in PD are organized based on the (presumed) pathophysiology, but lack a clear structure that can aid in the differential diagnosis. Adopting a systematic way of thinking about disturbed sleep facilitates the clinical interview and reduces the risk of missing sleep disorders. In Figure 1, we have put the various PD-related sleep disorders into a flowchart, which can be followed in every patient. The order is based on differential diagnostic grounds, and is not related to prevalence or severity. The various disorders are categorized into "excessive daytime sleepiness" and "disturbed nocturnal sleep". The latter category is in turn subdivided into "nocturnal motor symptoms", "sleep-related breathing disorders" and "other causes of insomnia".

The diagnostic process starts with determining whether daytime sleepiness is present. If so, one should decide if disturbed nocturnal sleep is a likely culprit, in which case the flowchart should be followed in that direction. If not, side-effects of medication and primary hypersomnias remain possible causes for excessive daytime sleepiness. Nocturnal motor symptoms are the primary cause to be checked when nighttime sleep is disturbed. Sleep-related breathing disorders should then be checked for. What remains are several other causes of insomnia, with their associated diagnostic trajectory. Importantly, one should always consider the fact that more than one sleep disorder can be present.

Table 3 explains the various categories of the flowchart, with the associated diagnostic tools. The table further shows in which cases the help of a sleep medicine specialist could be considered for additional diagnostic and therapeutic input.

Figure 1. Diagnostic flowchart for the assessment of sleep disorders in PD

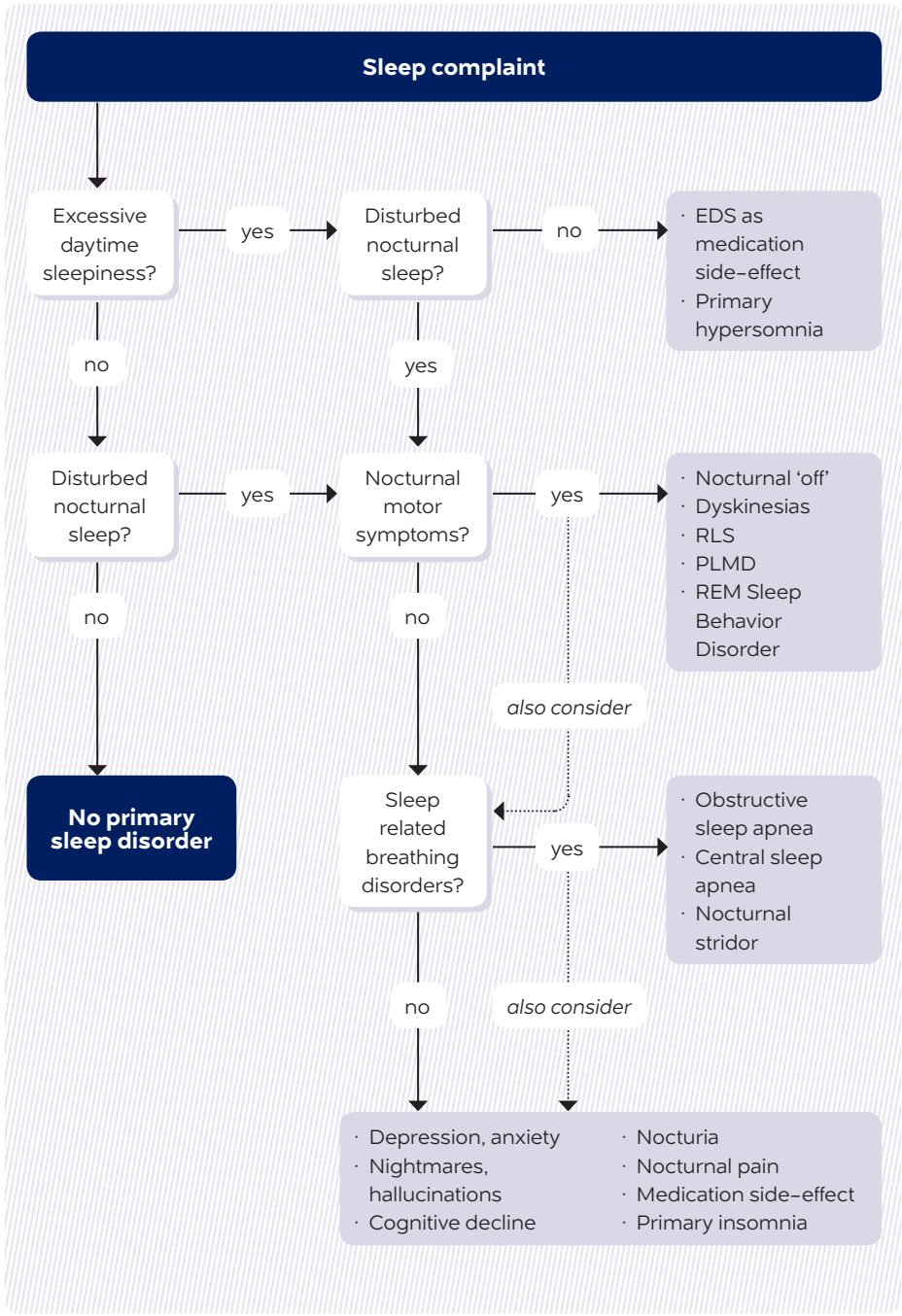








Table 3. Diagnostic outline for sleep disorders in PD

| Main sleep symptom | | Etiological category | Diagnostic strategy |
|---|---|---|---|
| daytime | Excessive Daytime Sleepiness | Disturbed nocturnal sleep (see *nighttime*) | |
| | | Medication side- effect | Clinical history, dedicated questionnaires (e.g. ESS), lower dose or change to different drug |
| | | Primary hypersomnia | Clinical history (exclusion of other causes), dedicated questionnaires (e.g. ESS), MSLT |
| night-time | Nocturnal Motor Symptoms | Nocturnal "off": tremor, rigidity, akinesia, dystonia | Clinical history, when in doubt: video-polysomnography |
| | | Dyskinesias | Clinical history |
| | | Restless Legs Syndrome | Clinical criteria, laboratory investigations (e.g. ferritin levels) |
| | | Periodic Limb Movement Disorder | Polysomnography (interpretation by sleep specialist) |
| | | REM Sleep Behavior Disorder | Clinical history, video-polysomnography |
| | Sleep Related Breathing Disorders | Sleep apnea syndromes (obstructive and/or central) | Clinical history, clinical examination, pulmonological evaluation, polygraphy/ polysomnograpy |
| | | Nocturnal stridor | Clinical history, polysomnography with synchronous audio recording, consider laryngoscopy |
| | Other causes of insomnia | Depression, anxiety | Clinical history, diagnostic questionnaires, assessment by psychiatrist |
| | | Nightmares, hallucinations, psychosis | Clinical history, assessment by psychiatrist |
| | | Cognitive decline and dementia | Neuropsychological tests, check underlying treatable causes |
| | | Nocturia | Clinical history, physical examination, urological evaluation |
| | | Nocturnal pain | Clinical history, screen for comorbidity, physical examination |
| | | Medication side-effects | Clinical history, lowering dose or change to different drug |
| | | Primary insomnia | Clinical history, exclusion of other causes |

*In darker blue: typical indications for consultation with a sleep medicine specialist ESS: Epworth Sleepiness Scale; MSLT: Multiple Sleep Latency Test*

# Different sleep problems

## Excessive daytime sleepiness

### Excessive daytime sleepiness versus "sleep attacks"

The most important characteristic of excessive daytime sleepiness (EDS) is the tendency to actually *fall asleep* during the day, usually accompanied by a "building" feeling of sleepiness. Prevalence rates of EDS in PD range from 29% to almost 60%.[8,11,32,35–37] The term "sleep attacks" is often intermingled with EDS, but this is not justified. Sleep attacks are sudden, irresistible sleep episodes, often without warning signs. In the late 1990s, Frucht et al. described sleep attacks in PD patients while driving, after starting treatment with dopamine agonists.[38] A large study from Canada, including 638 consecutive PD patients, showed a prevalence of sleep attacks while driving of 3.8%.[32] In only 0.7% of patients, sleep episodes occurred without any warnings signs. Sleep attacks can also occur during activities other than driving. Paus et al. reported sudden onset sleep while engaged in some form of activity (e.g. during a meal or phone call) in 580 of 2952 patients (19.6%).[39] Körner et al. suggested even higher prevalence rates, with sudden sleep episodes in 42.5% of 6620 PD patients, but only in 19.2% during activities.[40]

### Excessive daytime sleepiness versus fatigue

Although patients often describe EDS as "fatigue", these represent two distinct symptoms. Fatigue is a feeling of tiredness and lack of energy, but does not result in unwanted sleep episodes.[41] Moreover, EDS and fatigue are differentially associated with clinical features of PD.[37] Specifically, fatigue is associated with higher scores on the motor part of the Unified Parkinson's Disease Rating Scale (UPDRS III), higher Hoehn&Yahr stage and higher scores on a depression rating scale. Conversely, EDS is associated with disease duration and type of dopaminergic treatment; patients with non-ergot dopamine agonist had higher scores on the ESS.[37]

### Causes of excessive daytime sleepiness

Many studies have described a correlation between EDS and the use of dopaminergic drugs.[10–12] A recent study reported a dose-dependent effect of mean overall levodopa-equivalent dose and EDS, as measured with both ESS and MSLT. Importantly, this study analyzed the use of dopamine agonists, either alone or in combination with levodopa, but not levodopa alone.[35] However, some authors found no relation between EDS and medication, and concluded that sleepiness was related directly to PD pathology.[42] Recent studies focused on the possibility that EDS in PD may be related to damage to the hypothalamic sleep-regulating hypocretin system. Thus, Fronczek et al. found a significant decrease in the number of hypocretin neurons and a lower hypocretin-1 concentration in ventricular CSF in post-mortem material.[43] In the same issue of *Brain*, Thannickal et al. also described a decrease in hypocretin neurons, which correlated with disease stage.[44] Unfortunately, these pathological findings do not translate into a clinically useful test: one study reported low hypocretin-1 levels in spinal CSF in only two out of eight PD patients with EDS, and other research groups found normal spinal CSF levels.[35,45–47]







## Nocturnal motor symptoms

Nocturnal motor symptoms are an important cause of sleep disturbances in PD, and include nocturnal "off" symptoms and dyskinesias, in addition to primary sleep disorders such as restless legs syndrome (RLS), periodic limb movement disorder (PLMD) and REM sleep behavior disorder (RBD).

### Nocturnal "off"

Lees was the first to describe the phenomenon of nocturnal "off" in 1988, reporting that 65% of PD patients had difficulty turning around in bed.[2] Nowadays it is widely appreciated that nocturnal "off" symptoms contribute to impaired mobility in bed, making it difficult to turn around or find a comfortable sleep position. Surprisingly, no one has studied the influence of impaired bed mobility on sleep quality and sleep structure. The diagnosis of sleep problems caused by nocturnal "off" is primarily based on the clinical interview. There is a major need for objective measurements to diagnose sleep disturbances caused by nocturnal "off" periods. Recently, Bossenbroek et al. validated the use of a tri-axial accelerometer to measure the intensity of movements in addition to body position during sleep.[48] This seems to be a promising new way to objectively measure nocturnal "off" periods in PD, even in the home situation.

### Dyskinesias

Levodopa-induced dyskinesias are sometimes more intense in the evening, for example due to a cumulative effect of repeated doses of long-acting dopaminergic agents. Biphasic dyskinesias can also be severe in the evening after patients have taken their final evening dose of medication. Patients may report that these dyskinesias hamper the onset of sleep, or disturb sleep when dyskinesias return during nighttime arousals.[49] However, no formal data are available on the prevalence and influence of nocturnal dyskinesias on sleep in PD patients.

### Restless legs syndrome

The dopaminergic system plays an important role in the pathophysiology of RLS, so it is to be expected that the prevalence of RLS is increased in PD. However, this relation between RLS and PD is not completely clear. Epidemiological studies yielded conflicting results. Some authors reported increased RLS prevalence rates of up to 21% in Caucasian PD patients.[50] In contrast, a recent study could not confirm this high prevalence, although the study population was on relatively high levodopa doses, which may have influenced the outcomes.[51]

RLS and PD may share a therapeutic response to dopaminergic drugs, but other characteristics point to a differential or additional effect of PD pathology. Compared to idiopathic RLS patients, PD patients with RLS have a higher age of onset and less often a positive family history of RLS.[50] In addition, studies using transcranial sonography found a significantly decreased echogenicity of the substantia nigra in patients with idiopathic RLS compared to PD patients with or without RLS, and healthy controls.[52,53]

Regardless of the exact prevalence, it remains important to be vigilant for the presence of restless legs in PD, because RLS has a negative influence on quality of life, while the symptoms can often be treated satisfactorily. Note that specific PD symptoms – such as akathisia – may obscure the diagnosis of RLS. Therefore, it is important to adhere to the diagnostic guidelines which emphasize the presence of all four core features (Table 4).[54] Secondary RLS should be excluded using appropriate investigations. In the general population, iron deficiency is the most common cause of secondary RLS, and one study confirmed this association in PD patients with RLS.[30] Ferritin levels are the best marker for iron deficiency.[30,54]

### Periodic limb movement disorder

Periodic limb movement disorder (PLMD) often co-occurs with RLS, but is a distinct disorder. Literature on the presence of PLMD in PD is scarce. Arnulf et al. found PLMD in 15% of a PD patient cohort,[42] which is clearly higher than population estimates (which range around 8%).[55] Another study found more periodic limb movements in patients with PD compared to controls, but also compared to patients with MSA.[56] It is often assumed that periodic limb movements result in arousals from sleep, resulting in daytime symptoms. However, Arnulf et al. found no association between the presence of PLMD and daytime sleepiness.[42] Indeed, periodic limb movements are often asymptomatic, making it difficult to assess their clinical significance.[57]







**Table 4.** Diagnostic criteria for RLS[54]

**Required criteria**

- Uncomfortable and unpleasant sensations in the extremities (prickling, stinging, itching, “like crawling ants”, sometimes described as pain), with an urge to move
- The sensations begin or worsen during inactivity
- The sensations and/or urge to move are partially or totally relieved by movement
- The sensations and/or urge to move display a circadian pattern: worse in the evening or night compared than the early morning; or only occurring in the evening or night

**Supportive features of RLS**

- Positive family history
- Clear beneficial response to dopaminergics
- Presence of periodic limb movements during sleep

### REM sleep behavior disorder

RBD is a parasomnia resulting from loss of normal atonia during REM sleep, leading to vigorous behavior with enactment of vivid and frightening dreams. The excessive motor activity may even result in injuries to the patient or bed partner.[58] During the last decade RBD has shown to be a premarker of alpha synucleopathies such as PD.[59,60] The prevalence of RBD in PD is estimated between 15–30%.[58,61,62]

Given the potential dangers and available treatment options, asking every PD patient and the bed partner for the presence of “dream enactment” is recommended (see Table 1). Eisensehr et al. found frequent misdiagnoses when RBD is established solely upon the clinical interview.[63] As RBD also needs to be differentiated from other sleep disorders, such as obstructive sleep apnea, confusional arousals, nocturnal hallucinations and nocturnal frontal seizures, the threshold for doing a PSG should be low, even when the clinical interview is very typical.[64]

The gold standard for diagnosis remains a PSG with simultaneous audiovisual recording. Video-PSG allows a confident diagnosis by showing an increase of tonic and phasic muscle activity in REM sleep, sometimes associated with actual motor behavior. The “SinBar group” – a collaboration between the sleep groups in Innsbruck and Barcelona – introduced an EMG montage protocol, and showed that simultaneous recording of the m. mentalis, m. flexor digitorumsuperficialis in the up-

per limbs and m. extensor digitorum brevis in the lower limbs provides the highest rate of phasic EMG activity during REM sleep in patients with RBD.[65] More recent work evaluated the diagnostic performance of this EMG montage, showing a sensitivity of 94.4%, specificity of 47.2% and a negative predictive value of 41.9%.[66] Until recently, however, no formal cut-off values were available to determine when phasic or tonic EMG activity in REM sleep is "too high". In 2010, Montplaisir et al. established the first set of such parameters for idiopathic RBD which can be used in a clinical or research set-up.[67] In addition to EMG-based polysomnographic methods, a polysomnographic video-based scale is now available to rate the severity of RBD.[68]

In addition to its clinical relevance, RBD also sheds highly interesting new light onto the regulation of motor activity in PD. De Cock et al. found a restoration of normal motor control during nighttime movements in association with RBD. The majority of bed partners of PD patients with RBD (87%) observed an improvement in movement quality during RBD episodes (faster, stronger, or smoother).[69] Video-PSG studies indeed showed body movements during REM without obvious signs of parkinsonism during REM. The exact meaning of these observations remain unclear, but it was hypothesized that these movements are somehow generated in the motor cortex, thus bypassing the defective extrapyramidal systems.[69]

## Sleep-related breathing disorders

Sleep-related breathing disorders are relatively common among the general population. They are important to diagnose, as they may not only result in unrefreshing sleep and daytime sleepiness, but also negatively influence the long-term cardiovascular risk profile.

The most common forms of sleep-related breathing disorders are sleep apnea syndromes, divided into two types: obstructive sleep apnea (OSAS) and central sleep apnea. OSAS is characterized by repetitive episodes of complete or partial upper airway obstruction that occur during sleep. Two recent studies show no increased risk of OSAS in PD patients.[70,71] In fact, one study even found a lower prevalence (27% in PD, compared to 40% in controls referred for daytime sleepiness).[70] The frequency of sleep apnea did not differ between unselected PD patients and patients who were referred for sleepiness. Differences in patient population as well as selection of controls may explain the different results across studies.







Established risk factors for OSAS – such as increased neck circumference and retrognathia – obviously also apply to PD patients. However, there is no correlation between the presence of OSAS and snoring, sleepiness or elevated body mass index in PD.[71]

Although OSAS is not more prevalent in PD patients compared to controls, the prevalence rate is still 15–30%, so clinicians should remain vigilant for its presence.[70,71] The diagnostic yield of PSG versus limited respiratory polygraphy to detect sleep apnea in PD has not been studied. Given the complexity of sleep disturbances in PD with a high frequency of combined disorders, we advocate the use of full PSG whenever a sleep registration is deemed necessary.

### Nocturnal stridor

Nocturnal stridor is a specific sleep-related breathing disorder, that is mainly associated with multiple system atrophy.[72] Its presence has therefore differential diagnostic value in the workup of an extrapyramidal disorder. In addition, stridor is associated with a decreased life-expectancy.[73] Stridor can be recognized clinically as an inspiratory vocalization with a strained, harsh and high-pitched (260–330 Hz) sound during sleep. To formally diagnose nocturnal stridor, a PSG with audiovisual monitoring should be performed.

## Other causes of insomnia

When nocturnal motor symptoms and sleep-related breathing disorders are excluded, several other causes of disturbed nighttime sleep remain. Together, these may jointly be referred to as "insomnia". Up to 60% of PD patients complain about insomnia, especially sleep fragmentation and early morning awakenings.[4] Insomnia can take several different forms, manifesting as difficulty with initiating sleep, maintaining sleep, early-morning awakenings, or a combination of these. However, the diagnosis "insomnia" should be used with caution. "Insomnia" can have widely varying causes, and the generic term does not discriminate between them. In Figure 1, these causes of problems with sleep initiation or maintenance are listed.

## Conclusions

Sleep disorders are very common in PD, but still their recognition and diagnosis remains challenging. Our proposed diagnostic work-up can serve as a basis for tailored therapeutic interventions. The diagnostic armamentarium is extended and refined all the time, for example yielding well-validated clinical questionnaires, or new devices to measure body movements related to sleep in the home environment.







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# 2.2

## Importance of sleep for the patient with Parkinson's disease

**Published as**

**S**leep matters in Parkinson's disease:
use of a priority list to assess the presence of sleep disturbances
Louter M, Marck MA van der, Pevernagie DAA, Munneke M, Bloem BR, Overeem S.
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## Abstract

### *Introduction*

*Despite their high prevalence and clinical impact, sleep disorders in Parkinson's disease (PD) appear to receive insufficient attention in clinical practice. We compared the importance of sleep disorders relative to other symptoms and daily issues. Furthermore, we determined whether relevance as perceived by patients correlated with the subjective presence of sleep disruption scored with a rating scale.*

### *Methods*

*We studied a cohort of 153 consecutive patients (95 men) who were referred for problems other than sleep to our referral center. Prior to their visit, patients ranked their individual top 5 clinical priorities (out of 23 items), indicating the most problematic domains for which they requested medical attention. Additionally, nocturnal sleep quality and excessive daytime sleepiness were assessed with validated questionnaires.*

### *Results*

*The top three important domains according to the patient were movement (79.9%), medication (73.2%) and physical condition (63.4%). Sleep was the 6th most frequently reported item, marked by 37.9% of the patients. Among the patients who scored sleep as a priority, 47 (81%) had a poor sleep quality (Pittsburgh Sleep Quality Index >5). Although excessive daytime sleepiness was present in almost 30% of patients, a minority of them put it on their priority list.*

### *Conclusion*

*A priority list can be used to prioritize patient-centered quality of life issues. Our results show that sleep is a clinical priority for about one third of patients. Surprisingly, excessive daytime sleepiness was usually not prioritized by patients during the consultation, underscoring the need to use ratings scales alongside with subjective priorities.*








## Introduction

Sleep disorders are a frequent non-motor symptom in Parkinson's disease (PD), with an estimated prevalence of more than 70%.[1–4] Poor sleep quality has a profound impact on quality of life.[5,6] Sleep can be disturbed by a variety of reasons, ranging from insomnia to specific primary sleep disorders such as REM sleep behavior disorder.[3,4,7] The mechanisms underlying these various sleep disorders are heterogeneous.[8,9]

Despite their high prevalence and clear influence on quality of life, sleep disorders may receive insufficient attention in clinical practice.[10] Chaudhuri et al. studied the underreporting of non-motor symptoms in 242 PD patients.[10] To assess which non-motor symptoms were present, patients completed the Non Motor Symptom Questionnaire (NMSQuest) prior to their consultation.[11] After their visit, patients were asked if they had discussed the marked items on the NMSQuest during the consultation. Daytime sleepiness, insomnia, vivid dreams, acting out dreams or restless legs were present in up to 50% of patients, but 36–52% of these symptoms were not discussed during the consultation.[10]

The reason for this remains unclear. From the doctors' perspective, there may be insufficient knowledge regarding sleep disorders, or a lack of time during a routine consultation. However, there also seems to be underreporting from the patients' side. This does not mean that sleep is unimportant to patients. In the general population, sleep disruption creates a high disease burden and influences quality of life.[12–14] One explanation for the underreporting of sleep problems is that PD patients do not always recognize their sleep problems as a separate, treatable symptom, but merely regard it as a "normal" part of their disease.[10] It is also possible that patients do not consider their sleep problems to be a part of their PD at all, leading patients to think that their sleep issues should be discussed with another physician rather than the movement disorder specialist. Finally, the clinical phenotype of PD is very broad, involving a whole gamut of different motor and non-motor symptoms. Deciding which symptoms to address during the limited consultation time is understandably difficult.[10]

In this study, we addressed several aspects of sleep disorders in PD from a patients' perspective. We used a priority list to assess the relevance of sleep disorders in comparison to other symptoms and daily issues in PD. Furthermore, we determined whether relevance from the patients' view correlated with abnormal scores on sleep questionnaires.

# Patients and methods

## Setting and study population

For this study, consecutive patients were included who visited the Parkinson Centre Nijmegen (ParC), a tertiary referral centre. ParC can be consulted by local neurologists to assess specific diagnostic and treatment difficulties in patients with parkinsonian disorders. Because the prevalence and characteristics of sleep disorders vary between the different forms of parkinsonism, we here focused on patients with idiopathic PD. This diagnosis was made by experienced movement disorder specialists and based on the UK Brain bank criteria.[15] At our center, a comprehensive multidisciplinary team is available, including movement disorder specialists, physiotherapists, occupational therapists, and speech–language therapists.[16] Prior to their visit, patients completed questionnaires concerning all possible problem areas in PD, such as adequacy of treatment, movement, speech and sleep. At the end, patients were asked to indicate which symptoms and daily limitations particularly necessitated clinical attention, by composing a top 5 list of clinical priorities. The study was approved by the medical ethics committee of the Radboud University Medical Centre. All patients who were approached agreed in the use of their data for scientific purposes and gave informed consent for the study.

## Clinical characteristics

Demographic variables were recorded, including disease duration. Disease stage was rated using the Hoehn&Yahr (H&Y) staging system.[17] Dopaminergic treatment was quantified by calculating the Levodopa Equivalent Dose (LED) in mg/day.[18]

## Priority list

To tailor the clinical visit, patients were asked to draft a priority list of their own most problematic areas they particularly requested attention during the clinical interview and assessments. To indicate their priorities, patients could choose from a list of 23 items concerning all possible problem areas: living situation, medication advise, daily schedule, information on brain surgery, physical condition, memory, mood, behavior, sleep, autonomic dysfunction, drooling, speech, chewing and swallowing, nutrition, movement, transport, medical devices, self care, household activities, leisure activities, employment, social contacts and sexuality. Some of these issues, such as autonomic dysfunction, were further explained in the questionnaires and accompanied by examples. Patients were asked to score a maximum of five out of these 23 items.







## Sleep

To assess sleep quality we used the Pittsburgh Sleep Quality Index (PSQI).[19] The PSQI is a validated questionnaire frequently used in PD.[20,21] The questionnaire assesses different aspects of sleep such as subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep medication and daytime dysfunction. Sub scores on these areas are then combined to yield a total score that can range from 0 to 21. Poor sleep quality is indicated by a total PSQI higher than 5. Daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS).[22] The ESS is an easy to use questionnaire in which patients have to indicate the possibility to fall asleep in eight different situations. The ESS ranges from 0–24 and a score of >10 indicates excessive daytime sleepiness (EDS).

## Data analysis

All statistical analysis was done using SPSS for Windows version 18. To compare the importance of sleep to other problem areas in PD, the number of times an item was marked on the patients' priority list was counted and the results were ranked. In addition, the cohort was divided into patients who prioritized sleep and those who did not. To indicate if poor sleep quality and EDS are a reason to mark sleep as a priority, the presence of these problems was compared between both groups. Significance of comparison was calculated using t-test and chi-square test depending on the variable. Missing values were <5%, therefore all percentages are presented as valid percentages. All data are shown as mean±SD or N (%).

# Results

## Clinical characteristics

A total of 153 consecutive patients with PD were included (62.1% men). The clinical characteristics and mean scores on the PSQI and ESS are described in Table 1. Patients had an intermediate disease stage (majority at H&Y stage 2). There was a wide variety in use of levodopa and dopamine agonists. The LED ranged from 0–1300 mg/day, with a mean LED of 468.4±336.5 mg/day.

## Priority of problem areas

In 80 patients, more than five items were scored on the priority list. We decided to include all marked items in the ranking analysis, because re-analysis excluding these patients resulted in only minor shifts in the final ranking. The top three important domains that needed clinical attention according to the patient were movement

(79.9%), medication (73.2%) and physical condition (63.4%). About a third of patients (37.9%) prioritized sleep as an item they wanted to discuss during their visit (Table 2). Sleep was the 6th item on the list of 23 potential items. Among the non-motor symptoms, only memory problems scored slightly higher (66 patients, 43.1%). Clinical PD characteristics did not differ between patients who put sleep on their priority list and those who did not (Table 1).

### Prioritization in relation to nocturnal sleep quality

The mean score on the PSQI was 6.9±3.7. Poor sleep quality (PSQI >5) was present in 60.8% of patients. Patients who prioritized sleep had significantly worse sleep quality (PSQI 9.3±3.8 vs. 5.5±2.8, p<0.001, Table 1). Analyses of the PSQI scores suggested that this difference was mainly determined by subjective sleep quality, estimated sleep latency and habitual sleep efficiency (Table 1). Among patients who prioritized sleep as a problem, 81.0% actually had poor sleep quality (Table 3). Strikingly, among patients with poor sleep quality (PSQI >5), only 50.5% of patients put sleep on their priority list. In the subgroup of patients with the most disturbed sleep (indicated by a PSQI score >10), the majority of patients did report this as a problem (82.1%).

### Prioritization in relation to excessive daytime sleepiness

The mean score on the ESS was 8.0±5.2. EDS (ESS >10) was present in 29.7% of patients. Interestingly, patients who prioritized sleep had exactly the same ESS scores as patients who did not (8.0±5.2, Table 1). Among all patients who put sleep on their priority list, 18 (32.1%) had EDS (Table 3). Conversely, among patients with EDS, only 40.9% prioritized sleep as an item to discuss during consultation. Even in patients with more severe EDS (ESS>12), only 35.5% reported sleep as a priority.

### Prioritization in relation to overall sleep problems

To examine whether sleep problems in general (either nocturnal sleep problems, EDS, or both) were a reason to seek medical attention, we combined the PSQI and ESS results. This analysis showed that the vast majority (91.1%) of patients who prioritized sleep indeed had some form of sleep disturbance (PSQI >5, ESS >10 or both). However, many significant sleep problems remained undeclared: 49% of patients with nocturnal and/or daytime sleep dysfunction did not put sleep on their priority list (Table 3).







Table 1. Clinical characteristics

| | | Total | Sleep prioritized | Sleep not prioritized | p |
|---|---|---|---|---|---|
| Total | | 153 | 58 | 95 | |
| Gender man | | 95 (62.1%) | 32 (55.2%) | 63 (66.3%) | .168 |
| Age (yr) | | 65.9±9.7 | 66.3±8.8 | 65.6±10.2 | .679 |
| Disease duration (yr) | | 7.7±5.7 | 7.9±6.7 | 7.5±5.0 | .639 |
| LED (mg/day) | | 468.4±336.5 | 467.6±286.8 | 468.9±365.0 | .982 |
| Hoehn & Yahr | 1 | 8 (5.5%) | 1 (1.7%) | 7 (7.7%) | .648 |
| | 1.5 | 6 (4.1%) | 2 (3.7%) | 4 (4.4%) | |
| | 2 | 74 (51.0%) | 31 (57.4%) | 43 (47.3%) | |
| | 2.5 | 20 (13.8%) | 6 (11.1%) | 14 (15.4%) | |
| | 3 | 29 (20.0%) | 12 (22.2%) | 17 (18.7%) | |
| | 4 | 7 (4.8%) | 2 (3.7%) | 5 (5.5%) | |
| | 5 | 1 (0.7%) | – | 1 (1.1%) | |
| PSQI | | 6.9±3.7 | 9.3±3.8 | 5.5±2.8 | **<.001** |
| · PSQI sub scores | | | | | |
| · *Subjective sleep quality* | | 1.1±0.8 | 1.5±0.8 | 0.79±0.5 | **<.001** |
| · *Sleep latency* | | 0.9±1.1 | 1.5±1.2 | 0.6±0.8 | **<.001** |
| · *Sleep duration* | | 0.9±0.9 | 1.4±1.0 | 0.6±0.8 | **.014** |
| · *Habitual sleep efficiency* | | 1.0±1.2 | 1.7±1.2 | 0.6±0.9 | **<.001** |
| · *Sleep disturbance* | | 1.5±0.6 | 1.6±0.5 | 1.4±0.6 | .572 |
| · *Use of sleep medication* | | 0.5±1.0 | 0.6±1.1 | 0.5±1.0 | .280 |
| · *Daytimefunction* | | 1.1±0.7 | 1.3±0.7 | 1.1±0.8 | .713 |
| ESS | | 8.0±5.2 | 8.0±5.2 | 8.0±5.2 | .996 |

*Results are shown as mean ±SD or N (%).; LED = Levodopa Equivalent Dose, PSQI = Pittsburg Sleep Quality Index, ESS= Epworth Sleepiness Scale*

Table 2. Priority of problem areas among 153 patients with Parkinson's disease

| | Prioritized | | Prioritized |
|---|---|---|---|
| Movement | 122 (79.7) | Nutrition | 36 (23.5) |
| Medication | 112 (73.2) | Information about brain surgery | 33 (21.6) |
| Physical condition | 97 (63.4) | Behavior | 32 (20.9) |
| Memory | 66 (43.1) | Chewing/swallowing | 32 (20.9) |
| Speech | 59 (38.6) | Medical devices | 32 (20.9) |
| Sleep | 58 (37.9) | Leisure activity | 32 (20.9) |
| Autonomic dysfunction | 56 (36.6) | Self care | 28 (18.3) |
| Mood | 48 (31.4) | Daily schedule | 23 (15.0) |
| Sexuality | 44 (28.8) | Living situation | 21 (13.7) |
| Drooling | 43 (28.1) | Employment | 21 (13.7) |
| Transport | 39 (25.5) | Household activities | 20 (13.1) |
| Social contacts | 37 (24.2) | | |

*Results are shown as the number of patients who put the item on their priority list N (%)*

Table 3 Sleep problems as a reason to prioritize sleep

| Sleep quality | Sleep not prioritized | Sleep prioritized | Total |
|---|---|---|---|
| PSQI ≤ 5 | 49 | 11 | **60** |
| PSQI > 5 | 46 | 47 | **93** |
| | **95** | **58** | **153** |
| **Daytime sleepiness** | **Sleep not prioritized** | **Sleep prioritized** | **Total** |
| ESS ≤ 10 | 66 | 38 | **104** |
| ESS > 10 | 26 | 18 | **44** |
| | **92** | **56** | **148** |
| **Sleep problems** | **Sleep not prioritized** | **Sleep prioritized** | **Total** |
| No sleep problem | 39 | 5 | **44** |
| Sleep problem | 53 | 51 | **104** |
| | **92** | **56** | **148** |

*PSQI = Pittsburgh Sleep Quality Index; ESS = Epworth Sleepiness Scale*







## Discussion

Sleep matters for many patients with PD. Our results show that sleep problems are an important issue among other symptoms and daily limitations in PD. Especially poor nighttime sleep quality is a reason to call for medical attention. Surprisingly, EDS was rarely a reason to address sleep during the consultation, despite the apparent clinical impact.

### Sleep problems as a reason to prioritize sleep

As in previous studies, 70% of patients had a disturbed sleep.[1–4] 81% of patients who prioritized sleep as an item to discuss had poor sleep quality. Moreover, more than 90% had either poor sleep quality, EDS, or both. This indicates that when a patient marks sleep on his priority list, there is indeed a sleep problem and further analysis is warranted.

Remarkably, not all patients with sleep problems marked this on their priority list. One explanation is that patients do not recognize their sleep as being poor. They are not aware that their sleep disturbance is related to their PD, and possible treatment options exist.[23] Another possible explanation is that, although sleep is disturbed, other issues are more important at the time of consultation. Therefore patients do rate it within the five most important issues to discuss. This theory is supported by the fact that patients with the poorest sleep quality (PSQI >10) did prioritize sleep. Especially EDS alone was no reason to prioritize sleep for the majority of patients. Next to the other explanations, this could also be caused by the fact that patients, wrongly, do not perceive their EDS as a *sleep* problem. Symptoms are present during the day and patients may not associate EDS with nighttime disturbances. Moreover, patients often consider EDS equivalent to fatigue, which is in fact a different symptom.[24]

### Assessing problem areas from the patient perspective

In the last few years patient–centeredness has become increasingly important as determinant of good quality of care. Patients who receive more involvement in their care are more satisfied and more compliant.[25] Issues that are important for a patients' quality of life may well differ from those issues that are typically addressed by doctors, such as drug effectiveness.[26] One way to assess the different aspects involved in a patients' health–related quality of life is the use of quality of life rating scales, such as the Parkinson's disease quality of life rating scale (PDQL).[27] Completing and checking these questionnaires, however, can be time–consuming for both patient and physician. Moreover, although these scales give a good impres–

sion whether certain problems exist or not, they do not show whether such problems are relatively important for any specific patient. In clinical practice, a priority list can be used as a "patient-centered quality of life scale". By providing information on the issues that are important for a patient, such a list can also be used to guide the clinical consultation, and provide more directed clinical attention. We show that the relevance from the patients' view correlated with the actual presence and severity of sleep disruption.

A priority list was first used by Politis et al.[28] They assessed 265 consecutive PD patients to study which problem areas were most troublesome from a patients' perspective. In agreement with our data, sleep was in the top 10 of problem areas.[28] Furthermore, sleep was also one of the most important non-motor symptoms. In our results as well as those of Politis et al. motor symptoms, medication and physical condition still are very important subjects for total group of PD patients.[28] For specific patients however, other items can have higher priority to discuss. Both priority lists again point out the importance of addressing non-motor symptoms in a consultation. In their study Politis et al. compared the presence of symptoms in early (≤ 6 years disease duration) and advanced (> 6 years) patients.[28] As a post hoc analysis, we also made this comparison, but found no difference in the results of the ranking between both groups (data not shown).

## Study limits and future prospectives

Asking a PD patient to make a priority list of issues to discuss during the consultation seems a promising tool for patient-centered care and improvement of treatment. Our results are a step in studying the usefulness of such a list, showing that it indeed can pick up the presence of nocturnal sleep problems. Although patient-centeredness leads to better compliance, this does not directly imply better care. Future studies should assess of the use of priority lists leads not only to a better detection of sleep problems, but to a more focused and higher quality treatment as well. Such research may also take into account the possible interaction between problem areas in PD, such as the influence of detecting and treating mood problems on sleep quality. Our cohort consisted of a large group of consecutive PD patients who visited a tertiary center. This could have biased the population in terms of e.g. disease severity. However, the clinical characteristics of our study population did not differ from other clinical trials in PD.[29,30] Whether our results also apply to a different population (e.g. PD patients in homecare or a general hospital) should be studied in the future.







Eighty patients marked more than the requested maximum of 5 items on their priority list. In PD, possible hyperactivity of the substantia nigra may put a "brake" on cognitive responses and as a consequence lead to indecisiveness.[31] It is possible that this mechanism causes PD patients to have difficulty prioritizing their complaints. This may be a disadvantage of our priority list, which includes a broad range of possible symptoms related to PD. However, we feel that such apalette of explicit choices is necessary. Sleep disturbances and other (non-motor) symptoms are regularly unrecognized as a problem related to their disease by PD patients. The use of a list of specific problem areas may to some extent prevent underreporting of symptoms, which may occur when patients would be asked to make a list of problem areas by themselves.

Our results show that a priority list is a helpful tool in the detection of sleep disorders in PD patients. Whether a priority list can also be helpful in detecting other symptoms and problem areas in PD should be further investigated.

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# Impaired bed mobility

## in Parkinson's disease

# 3.1

## Subjective impaired bed mobility in Parkinson's disease

**Published as**

Nocturnal hypokinesia and sleep quality in Parkinson's disease

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## Abstract

### *Introduction*

*In clinical practice problems turning around in bed are considered to negatively influence sleep in parkinson's disease (PD), however this has not been studied. Here we studied the influence of nocturnal hypokinesia within a group of patients with PD.*

### *Methods*

*Clinical and demographic data were obtained. Nocturnal hypokinesia was assessed using question 35 of the Parkinson's Disease Quality of Life Questionnaire. The presence was rated on a 5–point Likert scale, ranging from 1="all of the time" to 5="never". The Pittsburgh Sleep Quality Index (PSQI) was used to quantify sleep quality, higher scores indicating poorer sleep quality.*

### *Results*

*Out of 240 patients, 135 had difficulties turning around in bed. PSQI scores were significantly higher in patients with nocturnal hypokinesia (mean±SD) (PSQI 7.7±4.1) compared to those without (PSQI 6.1±3.4, p=0.001). A regression model correcting for age, disease duration and Hoehn&Yahr stage showed a significant influence of nocturnal hypokinesia on sleep quality (R–squared = 0.042, standardized–beta = 0.163, p= 0.026). Finally, there was a linear relationship between frequency of nocturnal hypokinesia and sleep quality.*

### *Conclusion*

*This is the first study that documents that nocturnal hypokinesia negatively affects sleep quality in PD. Nocturnal hypokinesia therefore merits therapeutic attention, including optimal night–time dopaminergic treatment and education about turning strategies in bed.*








## Introduction

One of the major features of Parkinson's disease (PD) is hypokinesia, defined as abnormally diminished motor function or activity. Hypokinesia in PD can severely interfere with daytime activities.[1] Hypokinesia can also be present during the night.[2,3] Nocturnal hypokinesia is most typically reported by patients as having difficulties changing body position in bed. Complaints about bed mobility are often raised by PD patients. The estimated prevalence of subjective difficulties with turning around in bed ranges from 45% to more than 80%.[4–6] Objective assessment of nocturnal movements showed that compared to controls, PD patients had a reduced total amount of nocturnal movements in bed, and a longer duration of turning events at night.[7]

Nocturnal hypokinesia is likely one of the factors responsible for the high prevalence of sleep disturbances in PD.[4,8] Surprisingly, the exact relationship between nocturnal hypokinesia and sleep quality is not known. Stack et al. studied recumbent turning strategies in 39 PD patients, seven of whom were completely unable to turn in bed.[5] Sleep initiation and maintenance were comparable between these two groups. However, turning difficulties were not graded. Gjerstad and al. showed that problems turning around in bed increased with duration of PD over a study period of eight years.[6] Severity or prevalence of insomnia complaints did not increase, but no correlations were made between insomnia and nocturnal hypokinesia. Van Hilten et al. found that PD patients had a higher frequency of nocturnal hypokinesia compared to control subjects who had sleep maintenance problems.[9] However, this study found no difference in nocturnal hypokinesia between PD patients and controls with sleep initiation problems, so further work remains needed to understand this issue.[9]

To date, nothing is known about the possible association between sleep disruption and problems turning around in bed *within* a group of PD patients. We therefore studied a large cohort of patients with PD, looking specifically at the relation between sleep quality on the one hand, and the presence and frequency of nocturnal hypo–kinesia on the other.

# Patients and methods

## Setting and study population

The Parkinson Center Nijmegen (ParC) serves as a tertiary university referral center. Because of excellent collaboration with the surrounding hospitals, this center receives many referrals by local neurologists, including the entire spectrum of PD (ranging from de novo patients to complicated late-stage patients). For this study, we evaluated all consecutive PD patients who visited ParC in the year 2008.

## Clinical characteristics

Demographic variables were recorded, including disease duration. Disease stage was rated using the Hoehn&Yahr staging system.[10] UPDRS motor scores were not included in the analysis, because UPDRS rating was not a part of the routine assessment in this clinical setting. Dopaminergic treatment was quantified by calculating the Levodopa Equivalent Dose in mg/day.[11]

## Nocturnal hypokinesia

Nocturnal hypokinesia was rated using the patients' ability to turn around in the bed, which is the most prominent clinical expression, which can also be rated easily by the patient. We therefore used question 35 of the Parkinson's Disease Quality of Life Questionnaire (PDQL) which rates nocturnal hypokinesia as turning difficulties in bed.[12] Patients have to rate the question: "How often in the last 3 months did you have trouble with difficulties turning around in bed?" on a 5-point Likert scale, ranging from 1="all of the time" to 5="never".

## Sleep quality

To asses nocturnal sleep quality, we used the Pittsburgh Sleep Quality Index (PSQI),[13] a validated questionnaire which is frequently used in PD.[14–16] The questionnaire assesses different aspects of nocturnal sleep, including sleep latency, duration and efficiency, subjective sleep quality and use of sleep medication. Sub scores are combined to yield a total score that can range from 0 to 21. Higher scores indicate worse quality of sleep. PSQI scores can be compared between groups. In addition, the prevalence of "poor sleep quality" can be measured, indicated by a PSQI score > 5.[13]





## Quality of life

The PDQL is a validated questionnaire assessing quality of life in PD.[12] It contains 37 items in four sub scales: Parkinson symptoms, systemic symptoms, emotional functioning and social functioning. An overall score can be derived, with higher scores indicating better quality of life. The total score ranges from 37–185.

## Data analysis

All statistical analysis was done using SPSS for Windows version 18. Patients scoring 1–3 on item 35 of the PDQL were considered to have clinically relevant nocturnal hypokinesia. We then compared clinical variables and sleep quality between patients with and without nocturnal hypokinesia. For the total PDQL, we replaced the score on item 35 by the mean score in this item in all patients, as we used item 35 as the primary outcome to assess nocturnal hypokinesia. T- and chi-square tests were used depending on the variable, with the exception of H&Y stage, which was assessed using a Wilcoxon signed rank test. In addition, we constructed a multiple linear regression model to study the effect of nocturnal hypokinesia on sleep quality, in order to correct for confounding variables. Finally, the relation between PSQI scores and frequency rating of nocturnal hypokinesia was tested, using a linear regression model with trend analysis. Data are shown as mean±SD or N(%), unless otherwise stated.



# Results

## Clinical characteristics and prevalence of nocturnal hypokinesia

In total, 240 PD patients were included (Table 1). Nocturnal hypokinesia was present in 135 patients (56.3%) during the last 3 months. Table 1 compares the clinical characteristics between patients with and without nocturnal hypokinesia. Patients with difficulty turning around in bed were older, had a longer disease duration and more advanced disease, and used more dopaminergic treatment.

## Sleep quality

As expected, there was a high prevalence of poor sleep in the whole PD population, with almost 60% of patients having a PSQI >5. However, the prevalence of poor sleep was even higher in patients with nocturnal hypokinesia, as reflected by significantly higher mean PSQI scores (Table 1).

Linear regression analysis confirmed the influence of nocturnal hypokinesia on sleep quality (R-squared = 0.042, standardized-beta = 0.204, p=0.002). We corrected the

regression analysis for the clinical variables that significantly differed between the two groups (age, disease duration, H&Y stage and LED). In the corrected model, nocturnal hypokinesia still had a significant effect on PSQI total score (R-squared = 0.066, standardized-beta = 0.163, p=0.026).

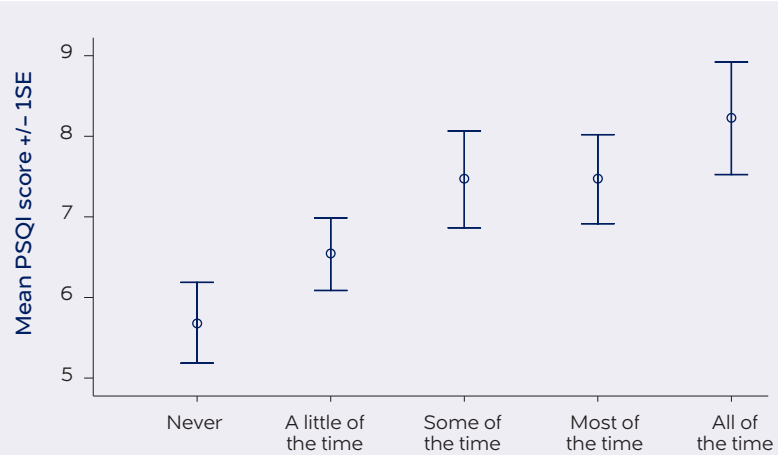
The relation between frequency of difficulties turning around in bed and sleep quality showed a linear trend (contrast estimate 1.9, p=0.001) (Figure 1). PSQI scores ranged from 5.7±3.6 in patients without nocturnal hypokinesia, to 8.2±4.7 in patients who always had difficulties turning.

Finally, we compared PSQI sub scores between patients with and without nocturnal hypokinesia. Patients with turning difficulties reported a worse subjective sleep quality, used more sleep medication, and had worse daytime functioning (Table 1).

## Quality of life

Overall quality of life was significantly better in patients without nocturnal hypokinesia compared to patients with nocturnal hypokinesia (142.5±18.1 vs. 120.5±19.6, p < .001). Nocturnal hypokinesia also negatively influenced the individual sub items of the PDQL (Table 1).

Figure 1. Linear regression model shows a linear trend of mean PSQI scores and frequency of nocturnal hypokinesia




*PSQI = Pittsburgh Sleep Quality Index*







Table 1. Clinical differences between patients with and without nocturnal hypokinesia

| | Total population | Nocturnal hypokinesia | No nocturnal hypokinesia | p |
|---|---|---|---|---|
| N | 240 | 135 (56.3%) | 105 (43.8%) | |
| Men | 146 (60.8%) | 68 (46.6%) | 78 (53.4%) | .272 |
| Age (yr) | 65.1±9.6 | 66.5±8.8 | 63.2±10.3 | **.008** |
| Disease duration (yr) | 7.7±5.5 | 9.1±5.7 | 5.8±4.8 | **<.001** |
| Hoehn 1 | 16 (7.0%) | 2 (1.6%) | 14 (14.0%) | **<.001a** |
| & Yahr 1.5 | 11 (4.8%) | 3 (2.3%) | 8 (8.0%) | |
| 2 | 107 (46.9%) | 55 (43.0%) | 52 (52.0%) | |
| 2.5 | 40 (17.5%) | 26 (20.3%) | 14 (14.0%) | |
| 3 | 44 (19.3%) | 32 (25.0%) | 12 (12.0%) | |
| 4 | 10 (4.4%) | 10 (7.8%) | – | |
| LED (mg/day) | 471.7±382.0 | 585.7±402.9 | 317.0±284.2 | **<.001** |
| Sleep quality | | | | |
| · PSQI* | 7.0±3.9 | 7.7±4.1 | 6.1±3.4 | **.001** |
| · PSQI > 5 | 141 (58.8%) | 87 (64.4%) | 54 (51.4%) | **.042** |
| · PSQI sub scores | | | | |
| · *Subjective sleep quality* | 1.13±0.80 | 1.27±0.83 | 0.96±0.73 | **.003** |
| · *Sleep latency* | 0.86±1.06 | 0.90±1.09 | 0.80±1.02 | .452 |
| · *Sleep duration* | 0.96±0.96 | 1.04±1.05 | 0.87±0.83 | .159 |
| · *Habitual sleep efficiency* | 0.93±1.15 | 1.01±1.17 | 0.84±1.11 | .275 |
| · *Sleep disturbance* | 1.46±0.59 | 1.54±0.58 | 1.36±0.57 | **.018** |
| · *Use of sleep medication* | 0.57±1.01 | 0.77±1.23 | 0.32±0.85 | **.001** |
| · *Daytime function* | 1.17±0.74 | 1.29±0.77 | 1.02±0.68 | **.004** |
| Quality of life | | | | |
| · PDQL | 130.3±22.0 | 120.5±19.6 | 142.5±18.1 | **<.001** |
| · PDQL sub scores | | | | |
| · *Parkinson symptoms* | 47.9±8.5 | 44.2±7.8 | 52.8±6.9 | **<.001** |
| · *Systemic symptoms* | 23.7±5.0 | 21.8±4.5 | 26.2±4.4 | **<.001** |
| · *Emotional functioning* | 32.9±6.2 | 31.1±6.2 | 35.4±5.3 | **<.001** |
| · *Social functioning* | 25.4±5.8 | 23.3±5.3 | 28.2±4.9 | **<.001** |

[a]*Wilcoxon W test *PSQI range 0-21*

## Discussion

Although important for many PD patients, the subject of nocturnal hypokinesia and sleep problems has thus far received little attention.[4–7] Here we show a clear detrimental influence of difficulties turning around in bed on the quality of nocturnal sleep. Our data suggest a direct link between hypokinesia and sleep disruption, as the results were not explained by other associated factors such as disease duration and stage. Furthermore, there was a relationship between the frequency of nocturnal hypokinesia and sleep quality.

Previous studies mostly compared PD patients with controls, and assessed hypokinesia and sleep quality separately. This limits the interpretation of these results, because nocturnal sleep disturbances in PD have a very heterogeneous pathophysiology. Our data point to an influence of turning difficulties on sleep quality per se, and highlight the importance of treating this symptomof PD. Although significant in several analyses, the main difference of 1.6 on the PSQI seems small. This is in part caused by the structure of the PSQI, where clinically relevant changes on a specific aspect of sleep (e.g. total sleep time) is mitigated in the overall score. However, as an example, a change of 1.6 in the total PSQI score can be caused by a reduction of total sleep time by two hours, which obviously is clinically significant.

Analysis of PSQI sub scores confirmed our main findings, showing subjectively worse sleep quality in patients with nocturnal hypokinesia. Furthermore, these patients used more sleep medication and experienced more daytime dysfunction in relation to poor sleep. In the PSQI, the need for medication to improve sleep is used as an indicator of bad sleep quality. Therefore, all medication patients take to improve sleep is taken into account, without specifying the type of medication used.

Interestingly, sleep latency did not differ between patients with and without nocturnal hypokinesia. This offers a possible explanation for the findings by van Hilten et al., who showed that problems turning around in bed did not differ between PD patients and controls with sleep initiation problems, while patients with sleep maintenance problems did have greater turning difficulties at night.[9] These results may be explained by greater severity of axial hypokinesia, not at the time when patients fall asleep, but which develops during the night, presumably because the action of most dopaminergic treatments is too short to cover the entire night. This finding suggests an indication for slow release preparations or continuous dopaminergic stimulation. We did not have information about administration times of the dopaminergic treatment, so the possible influence of night-time doses of dopaminergic agents on nocturnal hypokinesia could not be specifically addressed. The influence of dopaminergics on sleep is complex however, and to disentangle the specific effect on nocturnal hypokinesia may require future study. There is an effect on other sleep disorders in PD such as restless legs syndrome. On the other hand dopaminergic agents can for example cause hallucinations which can negatively influence sleep.







This study was not without shortcomings. First, selection bias may have affected our results. However, our population seemed representative of the general, “average” PD population in the community, with respect to age, disease duration and disease stage. Moreover, the reasons for referral to our center were highly diverse, and did not focus specifically on sleep problems. Still, almost 60% of patients had a PSQI score of more than 5, indicating significant sleep disturbances. This prevalence is in agreement with other (epidemiological) studies on sleep disorders in PD.[4,8,17,18] Compared to middle-aged adults, the mean PSQI score of our population was high.[19] Second, our results were based on subjective complaints of turning problems in bed. It will be very interesting to use more objective devices to quantify nocturnal hypokinesia in future studies, for example using actigraphy or pressure sensors. However, these devices have not been assessed for their ability to measure hypokinesia in PD, so formal validation studies are required first. A recent study showed promising results of a tri-axial accelerometer worn on the trunk, aiming to assess physical activity and body position during the night in healthy controls.[20] Such techniques should be used in future research to quantify nocturnal movements in PD, and further objectify our results showing a negative influence of hypokinesia on sleep quality. In addition, future studies should attempt to include other factors influencing sleep quality, such as other nocturnal movement disorders like restless legs syndrome and REM sleep behavior disorder. However, our data makes clear that in future studies assessing the complicated interaction between sleep-influencing factors in PD, nocturnal hypokinesia should be specifically taken into account.

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# 3.2

## Objective impaired bed mobility in Parkinson’s disease

**Published as**

Subjectively impaired bed mobility in Parkinson’s disease affects sleep efficiency

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## Abstract

### *Background*

*Impaired bed mobility may be an important reason for the high prevalence of insomnia in Parkinson's disease (PD). Here we assessed the influence of subjectively impaired bed mobility on both subjective and objective sleep parameters in insomnia PD patients with and without complaints of impaired bed mobility and controls with primary insomnia.*

### *Methods*

*We included 44 PD patients with sleep initiation or maintenance problems and 44 control subjects with primary insomnia. Sleep questionnaires, polysomnographic sleep parameters, activity data and number of body position changes were compared between PD patients and controls, and also within the PD group between patients with and without subjective complaints of impaired bed mobility (PD+IBM vs. PD−IBM).*

### *Results*

*54.5% of PD patients reported having impaired bed mobility. In the PD+IBM group, the number of body position changes was significantly lower than in PD−IBM (0.4/h (0.0–1.8) vs. 1.4/h (0.0–4.6), p=.015). Sleep efficiency was lower in PD+IBM patients (63.5, 26.2–85.6) compared to PD−IBM patients (78.4, 54.8–92.6, p<.001).*

### *Conclusion*

*PD patients who report impaired bed mobility have fewer sleep−related body position changes (i.e. nocturnal hypokinesia) than PD patients without such complaints. Furthermore, objective sleep efficiency is significantly diminished in these patients.*








## Introduction

Sleep disorders are of considerable burden to patients with Parkinson's disease (PD). Up to 90% of PD patients report some form of sleep problem.[1–3] Sleep can be disrupted by a wide variety of causes, and often multiple sleep disorders are present, including REM sleep behavior disorder, restless legs syndrome or sleep disordered breathing. Among the most prevalent sleep−related complaints in PD are difficulties with sleep initiation or maintenance, commonly referred to as "insomnia".[4–6] However, insomnia itself can have several different causes. For example, early morning awakenings can be related to an underlying depression. Nocturia can result in frequent awakenings throughout the night. Importantly, 45–80% of PD patients with insomnia report to have problems turning around in bed and finding a comfortable sleep position.[2,5,7] As such, subjectively impaired bed mobility may be one of the most important reasons for the high prevalence of insomnia in PD patients.[2,3,8]

The precise mechanism behind subjectively impaired bed mobility in PD is not clear. The complaint is often referred to as "nocturnal hypokinesia". In addition, pain and overall muscle weakness can hinder a patient finding a comfortable sleeping position.[9] Regardless of the mechanism, PD patients seem to have less body position changes during the night compared to the general population.[10] However, it remains unclear whether there is a relation between complaints of impaired mobility, actual number of body position changes and sleep quality. Such a relation would have clinical relevance, as decisions to start nocturnal dopaminergic therapy are often made based on a subjective complaint of impaired bed mobility.

In this study we assessed the influence of subjectively impaired bed mobility on objective sleep quality in patients with PD. Nocturnal body movements and sleep parameters were compared between insomnia PD patients with and without subjective complaints of difficulty turning around in bed. In addition these parameters were also compared between PD patients and controls with primary insomnia.

# Patients and methods

## Setting and study population

All patients were recruited from the outpatient clinic of the Sleep Medicine Center Kempenhaeghe, the Netherlands, a tertiary center for patients with sleep disorders. At this center, PD patients are seen in a dedicated program with a consultation followed by attended video-polysomnography that night.

Over a 2-year period, we included 44 consecutive PD patients with a primary complaint of sleep initiation or maintenance problems (insomnia). All patients were referred to our sleep center as part of their regular care. Only patients with idiopathic PD were included. As a control group, we included 44 patients with primary psychophysiological insomnia who received a nocturnal polysomnography as part of their clinical workup. Insomnia patients in whom a primary nocturnal sleep disorder (such as sleep disordered breathing) was found, were excluded. The study was performed according to the guidelines of the Medical Ethical Committees of The Netherlands. All patients gave informed consent.

## Clinical characteristics

Using a semi-structured interview, PD patients were divided in those with a subjective complaint of impaired bed mobility, and those without. Demographic and clinical characteristics were recorded, including disease duration. Disease stage was rated using the Hoehn&Yahr staging system during the "on" phase.[11] Overall dopaminergic treatment was quantified by calculating the Levodopa Equivalent Dose (LED) in mg/day.[12] In addition, nocturnal dopaminergic treatment was estimated by the dopaminergic dose taken before going to bed in LED (LED-night).

## Sleep questionnaires

Subjective sleep quality was measured using the Pittsburg Sleep Quality Index (PSQI).[13] The questionnaire assesses different aspects of nocturnal sleep, including sleep latency, duration and efficiency, subjective sleep quality and use of sleep medication. Sub scores are combined to yield a total score that can range from 0 to 21. Higher scores indicate worse quality of sleep. "Poor sleep quality" is defined as a PSQI score > 5.[13] Daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS).[14] The ESS is an easy to use questionnaire in which patients have to indicate the possibility to fall asleep in eight different situations. The ESS ranges from 0-24 and a score of >10 indicates excessive daytime sleepiness (EDS).







In the PD patients we additionally administered two sleep scales specifically designed for PD; the Parkinson"s Disease Sleep Scale (PDSS) and the SCOPA-sleep.[15,16] The PDSS is a visual analog scale addressing 15 items concerning sleep such as general sleep quality, daytime sleepiness and nocturnal movements. The scores on the separate items can be converted to a total score ranging from 0-150, with higher scores indicating better sleep quality.[15] The SCOPA-sleep contains two sections, assessing nocturnal symptoms and daytime sleepiness respectively.[16] In addition, there is a final single question rating overall sleep quality.

## Polysomnography

All patients underwent one night of supervised video-polysomnography (PSG), using a dedicated recording system (Schwarzer AHNS, PelviTec BV, Delft, The Netherlands), scored with BrainRT software (BrainlaB, OSG, Rumst, Belgium). PSG registration included electroencephalography, electromyography of m. submentalis and both m. tibialis anterior, electrooculography, electrocardiography and a full respiratory montage. Sleep stages were scored using the AASM 2007 criteria.[17] The main sleep outcomes were total sleep time (TST), sleep efficiency (SE), sleep latency, percentage of time in a specific sleep stage and number of awakenings per hour of sleep. Body position and movements were recorded using a position sensor placed on the thorax. Body position changes were verified using the video signal. Afterwards, total number of body position changes was determined. Actual number of body positions changes per night are influenced by the total sleep time, therefore the number of body position changes per hour was calculated. The outcomes were divided in body position changes per hour of sleep, per hour awake and per hour of the total time in bed. A turn causing a short awakening of maximum 30 seconds, directly followed by sleep was defined as a turn during sleep.

## Actigraphy

All PD patients underwent a night of actigraphy simultaneously with the PSG. The activity watch (Actiwatch, Cambridge Neurotechnology Ltd, Cambridgeshire, United Kingdom) was worn on the least affected side. Activity data were synchronized with the sleep stages recorded by the PSG. For each patient the frequency of activity periods during sleep and wake was determined. Finally the duration of the activity period and the level of activity was calculated.

## Data analysis

All statistical analyses were done using SPSS for Windows version 18. Scores on sleep questionnaires, PSG data and actigraphy were compared between PD pa-

tients with and without subjective complaints of impaired bed mobility. In addition, sleep outcomes and frequency of body position changes were compared between PD patients and a control group with primary insomnia. Finally, an exploratory analysis was performed on the relation between sleep quality and body position changes in PD patients, comparing patients with small and large numbers of nocturnal body position changes.

Data were not normally distributed according to Kolmororov–Smirnov testing. Therefore, statistical comparisons were performed using the independent–samples Mann–Whitney–U test. Data are shown as median (range) and N (%). All results were of two–tailed tests, significance level was set at p <.05.

## Results

### PD patients with and without impaired bed mobility

#### Clinical characteristics

Of the 44 PD patients with insomnia, 24 (54%) also complained of impaired bed mobility with difficulties turning around or finding a comfortable sleep position. The 20 other patients did not report such problems. The main type of insomnia in PD+IBM patients comprised of sleep maintenance problems, as present in 23 (95.8%) of the patients. Eight (33.3%) PD+IBM patients solely had sleep maintenance problems, 2 (8.3%) sleep maintenance as well as initiation difficulties, 6 (25.0%) sleep maintenance problems and early morning awakenings, and 6 (25.0%) complained of all three types of insomnia. Within the PD–IBM group, sleep maintenance problems were also the most common type, present in 16 (80.0%) subjects. Four (20%) patients only had sleep maintenance problems, 3 (15%) both sleep initiation and maintenance difficulties, 7 (35%) sleep maintenance problems and early morning awakenings, and 2 (10%) all three forms of insomnia. Presence of sleep maintenance problems was not significantly higher in PD+IBM compared to PD–IBM (Chi–squared 2.715, p = .099). Table 1 compares the demographic and disease characteristics between PD patients with and without subjective impaired bed mobility (PD+IBM versus PD–IBM). With the exception of disease stage, PD parameters were worse in de PD+IBM group, with longer disease duration and higher doses of dopaminergic medication during the day. Dopaminergic medication taken at bed time however was not higher. In the PD+IBM group, the prevalence of REM sleep behavior disorders was higher.







Table 1. Demographic and clinical characteristics of PD patients with and without impaired bed mobility

| | PD+IBM | PD–IBM | p |
|---|---|---|---|
| N | 24 | 20 | |
| Men (%) | 14 (58.3) | 14 (70.0) | .423 |
| Age (yr) | 62.5 (50.0–74.0) | 60.0 (36.0–82.0) | .402 |
| Disease duration (yr) | 7.0 (1.0–22.0) | 2.5 (0.5–7.0) | **<.001** |
| LED (mg/day) | 1143.8 (593.8–2557.5) | 655.0 (0.0–1854.0) | **.001** |
| LED–night (mg/before sleep) | 125.0 (93.8–250.0) | 93.8 (62.5 –187.5) | .125 |
| Hoehn & Yahr | | | .149 |
| 1 | 2 (8.3) | 1 (5.0) | |
| 1.5 | 1 (4.2) | 3 (15.0) | |
| 2 | 11 (45.8) | 14 (70.0) | |
| 2.5 | 4 (16.7) | 1 (5.0) | |
| 3 | 6 (25.0) | 1 (5.0) | |
| Other sleep diagnoses | | | |
| · OSAS (%) | 4 (16.7) | 7 (35.0) | .162 |
| · RBD (%) | 17 (70.8) | 8 (40.0) | **.040** |
| · RLS (%) | 7 (29.2) | 3 (15.0) | .264 |
| · PLMD (%) | 8 (33.3) | 4 (20.0) | .323 |
| · Mean activity score | 10.4±11.5 | 7.2±5.4 | .231 |

*Results are shown as median(range) or N (%). ; IBM+ = with impaired bed mobility; IBM– = without impaired bed mobility.; LED = Levodopa Equivalent Dose; LED–night = LED of dose before sleep; OSAS = obstructive sleep apnea; RBD = REM sleep behavior disorder; RLS = restless legs syndrome; PLMD = periodic limb movement disorder.*

#### Sleep parameters

There were no differences in subjective nocturnal sleep quality or daytime sleepiness between PD patients with and without complaints of impaired bed mobility (Table 2). When assessing the PDSS subdomains, PD+IBM patients rated higher on the sub score " nocturnal motor symptoms", which includes painful cramps, dystonia and tremor (Table 2). PSG analyses also revealed differences in objective sleep parameters. Total sleep time and sleep efficiency were significantly lower in

the PD+IBM group. This was also reflected by a higher number of awakenings and a larger percentage spent awake at night. Actigraphy showed no difference between activity periods, duration of periods and activity levels during sleep or wake between PD+IBM and PD–IBM (Table 2).

### Body position

The distribution of static body positions was not different between PD+IBM and PD–IBM groups. Bed mobility however was significantly diminished in PD+IBM, with a reduction of more than 70% of number of body position changes during sleep (Table 2). Interestingly, the frequency of body turns during wake at night was not different between groups, although this would be the period during which patients would actually note their problems with bed mobility (Table 2).

**Table 2. Subjective and objective sleep quality and body movements in PD patients with and without impaired bed mobility**

| | PD+IBM | PD–IBM | p |
|---|---|---|---|
| N | 24 | 20 | |
| **Sleep questionnaires** | | | |
| · PSQI | 13 (5–18) | 10 (5–19) | .364 |
| · PSQI>5 | 22 (95.7) | 19 (95.0) | .919 |
| · ESS | 6 (0–22) | 11.5 (4–18) | .160 |
| · ESS>10 | 7 (30.4) | 11 (55.0) | .103 |
| · PDSS | 77.0 (47.8–100.8) | 84.3 (53.5 –116.3) | .083 |
| · *Overall sleep quality* | 3.2 (0.2–8.9) | 3.1 (0.4–7.2) | .821 |
| · *Insomnia* | 8.7 (0.6–18.4) | 10.2 (1.9–16.2) | .184 |
| · *Nocturnal restlessness* | 7.6 (1.8–16.2) | 10.2 (0.6–19.4) | .811 |
| · *Nocturnal psychosis* | 14.2 (7.6–19.0) | 15.3 (3.7–20.0) | .914 |
| · *Nocturia* | 10.1 (3.3–18.4) | 10.2 (8.6–17.4) | .744 |
| · *Nocturnal motor symptoms* | 19.7 (9.6–33.7) | 28.4 (9.5–34.9) | **.021** |
| · *Sleep refreshment* | 2.1 (0.6–9.1) | 2.6 (0.3–8.4) | .930 |
| · *Daytime dozing* | 7.3 (1.3–9.8) | 7.4 (0.9–9.7) | .865 |
| · SCOPA–NS | 11.5 (3–15) | 8 (3–15) | .138 |
| · SCOPA–DS | 4 (0–16) | 8 (1–16) | .171 |







**Table 2. Continued**

| | PD+IBM | PD–IBM | p |
|---|---|---|---|
| **Polysomnography** | | | |
| · TST (min) | 298.0 (103.0–419.0) | 379.6 (243.0–530.0) | **.001** |
| · SE (%) | 63.4 (26.2 –85.6) | 78.4 (54.8–92.6) | **<.001** |
| · Sleep latency (min) | 9.7 (2.2–45.6) | 6.6 (1.3–41.6) | .383 |
| · N1 (%) | 11.5 (1.9–49.8) | 11.3 (1.1–(29.1) | .465 |
| · N2 (%) | 59.1 (22.2–90.3) | 54.9 (42.9–79.9) | .925 |
| · N3 (%) | 15.1 (0.0–72.4) | 15.9 (0–33.3) | .555 |
| · REM (%) | 12.3 (0.0–34.2) | 12.5 (2.0–31.4) | .768 |
| · Wake (%) | 33.5 (13.7–73.7) | 20.5 (4.7–45.2) | **<.001** |
| · Awakenings/hour sleep | 5.7 (3.2–32.0) | 4.5 (2.0–9.7) | **.005** |
| **Actigraphy** | | | |
| · Sleep | | | |
| · *Frequency of activity periods/hour* | 1.6 (0.0–7.9) | 1.4 (0.0–9.3) | .604 |
| · *Duration of activity periods (min)* | 2.3 (1.4–6.0) | 2.2 (0.5–4.2) | .780 |
| · *Level of activity periods* | 406,0 (0.0–111801.9) | 433.0 (0.0–22400.5) | .950 |
| · Wake | | | |
| · *Frequency of activity periods/hour* | 5.7 (2.7–17.2) | 5.6 (0.0–25.3) | .553 |
| · *Duration of activity periods (min)* | 5.5 (2.3–22.2) | 6.0 (2.2–13.2) | .958 |
| · *Level of activity periods* | 7882.5 (342.0–28646.3) | 6969.7 (0.0–44077.7) | .587 |
| **Body position changes** | | | |
| · Turns/hour during sleep | 0.4 (0.0–1.8) | 1.4 (0.0–4.6) | **.015** |
| · Turns/hr during wake at night | 6.2 (0.3–14.1) | 7.0 (0.0–16.5) | .172 |
| · Turns/hour during total night | 6.6 (0.3–15.0) | 8.1 (0.0–19.1) | .099 |

*Results are shown as median(range) or N (%).*

*PSQI = Pittsburgh Sleep Quality Index; ESS = Epworth Sleepiness Scale; PDSS= Parkinson's Disease Sleep Scale; SCOPA–NS/DS= SCOPA–sleep night symptoms/daytime sleepiness TST = total sleep time. SE = sleep efficiency. N1 (N2, N3) = percentage in stage 1 (2,3) sleep. REM = percentage in REM sleep.*

## PD patients versus controls with primary insomnia

### Clinical characteristics

Table 3 shows the clinical characteristics of the PD patients compared to the insomnia controls. Patients with primary insomnia were significantly younger than the PD patients. However, for all outcome measures, correction for age using a linear regression model did not change the results.

### Sleep parameters

The scores on sleep questionnaires and the PSG data for both groups are represented in Table 4. In both groups, the insomnia complaint was confirmed by a PSQI score above threshold. Insomnia controls reported an even worse subjective sleep quality as assessed by the PSQI than PD patients.

Excessive daytime sleepiness (ESS>10) however was more common in PD patients. Interestingly, PSG data revealed that PD patients had a significantly worse sleep efficiency and a shorter total sleep time than insomnia controls (Table 4). The percentage of time awake during the night was almost twice as high in PD patients. This difference was mainly caused by the PD+IBM subgroup. Comparing TST and SE between PD-IBM patients and controls showed no significant differences (TST: PD-IBM 379.6 (243.0-530.0) vs. controls 400.5 (195.0-519.0), p= .448; SE: PD-IBM 78.4 (54.8-92.6) vs. controls 82.4 (4.8-98.8), p= .201).

### Body position changes

Lying in bed, PD patients spent a larger percentage of time in a supine position than insomnia controls (PD 41%±30.4 vs. control 23.6% 17.3, p.046), the latter spending more time laying prone (PD 6.8%±13.6 vs. control 15.3±18.9, p=.026). Both groups displayed a wide range in the frequency of body position changes during the night, but although a difference was seen between turns per hour during the total night, this difference was only marginally significant. Furthermore, no difference was found between turns during sleep and during wake (Table 4).

## Influence of turns on sleep efficiency and total sleep time

To further analyze the influence of turning in bed on sleep quality we divided the PD group in "frequent" (n=19) and "rare" (n=25) turners. The cut-off between these groups was set at the mean number of turns per hour sleep in the total group (i.e. 1.0 turns/hour). PSG data did not differ between these groups, suggesting that the actual number of body position changes per se does not influence sleep quality (total sleep time: rare turners 311.9 min (103.0-439.0) vs. frequent turners 358.5 min (130.5-530.0), p =.112; sleep efficiency : rare turners 66.3% (26.2-60.0) vs. frequent turners 69.6%







**Table 3.** Clinical characteristics of PD and insomnia controls

| | PD | Controls | p |
|---|---|---|---|
| N | 44 | 44 | |
| Men (%) | 28 (63.6) | 25 (56.8) | .513 |
| Age (yr) | 61.0 (36.0-82.0) | 45.0 (21.0-64.0) | **<.001** |

*Results are shown as median (range) or N (%).*

**Table 4.** Subjective and objective sleep quality and body movements in PD patients versus insomnia controls.

| | PD | Controls | p |
|---|---|---|---|
| N | 44 | 44 | |
| Sleep questionnaires | | | |
| · PSQI | 11 (5-19) | 14 (6-19) | **<.001** |
| · PSQI>5 (%) | 41 (95.3) | 43 (100.0) | .152 |
| · ESS | 10 (0-22) | 4 (0-17) | **<.001** |
| · ESS>10 (%) | 18 (41.9) | 8 (18.6) | **.019** |
| Polysomnography | | | |
| · TST (min) | 332.5 (103.0-530.0) | 400.5 (195.0-519.0) | **<.001** |
| · SE (%) | 68.4 (26.2-92.6) | 82.4 (4.8-98.8) | **<.001** |
| · Sleep latency (min) | 8.5 (1.3-45.6) | 12.0 (1.5-251.5) | .094 |
| · N1 (%) | 11.3 (1.1-49.8) | 8.8 (2.2-28.7) | .059 |
| · N2 (%) | 57.1 (22.2-90.3) | 57.1 (39.4-80.2) | .716 |
| · N3 (%) | 15.2 (0.0-72.4) | 15.4 (0.0-39.0) | .632 |
| · REM (%) | 12.3 (0.0-34.2) | 17.3 (1.5-33.4) | **.001** |
| · Wake (%) | 30.0 (4.7-73.7) | 16.2 (1.2-62.1) | **<.001** |
| · Awakenings/hour | 5.5 (2.0-32.0) | 3.9 (0.6-8.6) | **.001** |
| Body position changes | | | |
| · Turns/hour during sleep | 0.6 (0.0-4.6) | 0.7 (0.0-6.6) | .770 |
| · Turns/hour during wake at night | 6.6 (0.0-16.5) | 7.9 (2.0-47.6) | .058 |
| · Turns/hour during total night | 7.6 (0.0-19.1) | 8.8 (2.0-47.6) | .046 |

*Results are shown as median(range) or N (%).; PSQI = Pittsburgh Sleep Quality Index; ESS = Epworth Sleepiness Scale; TST = total sleep time. SE = sleep efficiency. N1 (N2, N3) = percentage in stage 1 (2,3) sleep. REM = percentage in REM sleep.*

(31.3–92.6), p=.413). These results were supported by the finding that no significant correlation was found between turns during sleep and sleep efficiency in PD+IBM, PD–IBM and insomnia controls (Figure 1). Apparently, the subjective complaint of impaired bed mobility is more likely to influence sleep quality, rather than the actual number of body position changes itself. Indeed, when patients with and without complaints of impaired bed mobility were compared in both the rare and frequent turners, total sleep time and sleep efficiency were diminished in the PD+IBM group (Table 5).

Figure 1. Correlation between turns during sleep and sleep efficiency in PD+IBM, PD–IBM and controls

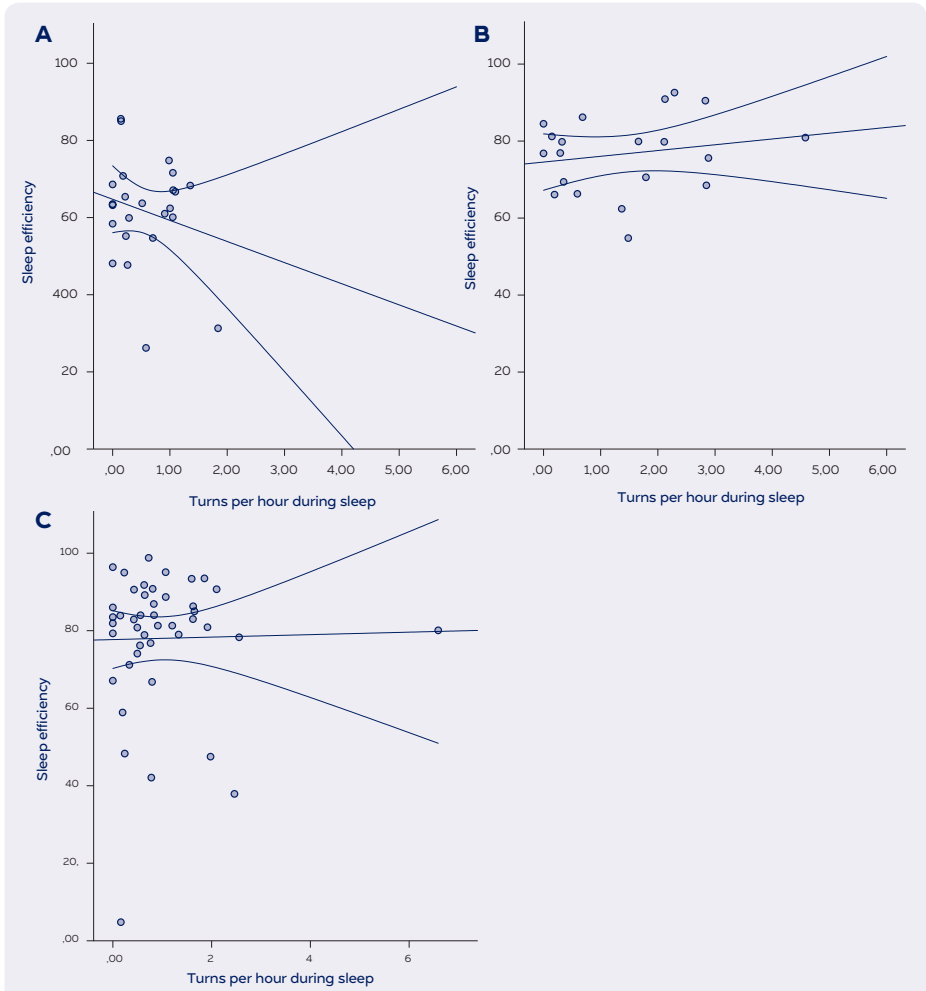






Table 5. Sleep parameters in “rare” and “frequent” turners with and without impaired bed mobility

| | | IBM+ | IBM– | p |
|---|---|---|---|---|
| Rare turners | N | 17 (65.4%) | 9 (34.6%) | |
| (<1.0 turn/hour) | TST (min) | 282.8 (103.0–419.0) | 370.5 (296.0–439.0) | **.009** |
| | SE (%) | 63.2 (26.2–85.6) | 76.9 (66.1–86.2) | **.005** |
| Frequent turners | N | 7 (38.9%) | 11 (61.1%) | |
| (≥1.0 turns/hour) | TST (min) | 329.0 (130.5–419.0) | 380.0 (243.0–530.0) | .077 |
| | SE (%) | 66.7 (31.3–71.6) | 79.8 (54.8–92.6) | **.018** |

*Results are shown as median (range) or N (%).*

*TST = total sleep time. SE = sleep efficiency.*



## Discussion

In this study, we show that PD patients who complain of subjectively impaired bed mobility move less during sleep, and have a significantly diminished sleep efficiency and total sleep time compared to patients without complaints. However, there is a broad range in the frequency of body position changes, and even subjects with almost no shifts in body position do not necessarily have impaired sleep quality. No correlation was found between turns during sleep and sleep efficiency. Among both rare and frequent turners, subjective complaint of impaired bed mobility determined the actual sleep disruption. This suggests that the subjective complaint of impaired bed mobility rather than the actual number of body position changes is related to insomnia.

Previous studies have suggested that impaired bed mobility negatively influences sleep quality.[8,18] Van Hilten et al. compared PD patients with healthy controls, showing that in a cohort with sleep maintenance problems, turning problems were more frequent in the PD group. This suggest that difficulty turning interferes with sleep.[18] However, these results could also be explained by a co–occurrence of both insomnia and impaired bed mobility in PD, without a causal relation. Recently we compared subjective sleep quality and impaired bed mobility *within* a large cohort of PD patients, showing that subjective sleep quality was significantly worse in those patients with impaired bed mobility.[8] The results of the present study objectively confirm this

negative association of impaired bed mobility on sleep: total sleep time and sleep efficiency were both significantly worse in PD patients with subjectively impaired bed mobility compared to those without. Moreover, the impact of impaired bed mobility on sleep is underlined by the fact that no differences were present in total sleep time and sleep efficiency between PD–IBM patients and controls. Remarkably, the differences in body position changes for the PD+IBM and PD–IBM were found during sleep, and not during wake. This is in contrast to what would be expected based on clinical findings. PD+IBM patients complain of having problems finding a comfortable sleeping position keeping them from falling asleep. Our results however show no difference during this awake period. Suggesting that the insomnia is influenced by the subjective feeling rather than the actual number of body position changes.

Other studies report increased nocturnal activity levels in PD patients compared to controls.[19,20] Possible explanations for this are sleep fragmentation leading to more wake or presence of specific nocturnal motor disorders such as REM sleep behavior disorder. Although our results show a significant increase in wake time in PD+IBM compared to PD–IBM we did not find differences between activity frequency, duration or level during sleep or wake between both groups. Our controls did not have actigraphy so a comparison between PD and controls could not be made.

A limited number of studies focused on actual nocturnal movements in PD. Laihinen et al. compared bed mobility in 9 PD patients and 11 neurological healthy controls, using a static charge sensitive bed to indicate the presence of possible turn–over events at night.[10] Movements were distributed in duration classes of <5 sec, 5–10 sec, 11–15 sec, >15 sec. The results showed that overall, PD patients had fewer movements compared to controls, and turning events were almost 20 sec shorter in PD patients.[10] In our study we show that nocturnal body movements in PD patients with insomnia are also less frequent than body position changes in patients with primary insomnia, but differences were small. We did find that PD patients spent a longer period of time lying supine than controls, which is in agreement with recent findings of Valko et al..[21]

The role of body position changes during sleep is rarely addressed in research. The general opinion is that diminished activity during the night is associated with poorer sleep quality. However, our data show that this is not necessarily the case: no correlation was found between sleep efficiency and turns during sleep. Moreover, several patients with few body movements during sleep did not have low sleep efficiency. In addition in clinical practice, subjects with primary insomnia tended







to move more during sleep. Our control group consisted of patients with primary insomnia, which could have resulted in a higher number of body position changes per hour in this group. The PD patients however also suffered from insomnia, which probably abolishes this problem. Nocturnal movements and activity during the night are most likely very different in each individual and may be influenced by a wide variety a variables such as age, the use of hypnotics and underlying disease. It is therefore difficult to determine what a normal frequency of body position changes during sleep means. One may hypothesize that PD patients should in fact turn more during sleep than controls, e.g. because of pain and/or rigidity. This would mean that the difference in turning events between PD patients and controls may in reality even be larger.

The precise mechanism of impaired bed mobility is not clear. Problems turning in bed are probably a part of the overall axial motor impairments in PD.[11] Rigidity, hypokinesia as well as bradykinesia are considered to play a role. Steiger et al. found an association between difficulty turning in bed and both axial rigidity and whole body bradykinesia in 19 PD patients. After levodopa treatment the turning in bed improved as well as the axial rigidity and bradykinesia.[9] This however is in contrast to the findings of Lakke et al. describing patients with turning difficulties when lying recumbent. Levodopa therapy improved rigidity and bradykinesia, but turning difficulties remained.[22–24] Lakke et al. stated that these turning problems were probably caused by “axial apraxia” rather than rigidity or bradykinesia in these patients.[6,12,22] Our results show that there is a group of patients with a small number of body position changes during the night, but without subjective complaints. To get more insight into the mechanism of impaired bed mobility this particular group should be further studied. It would for example be interesting to know whether impaired bed mobility is associated with a specific type of PD (eg. postural– instability gait difficulties vs. tremor dominant) or is associated with the degree of bradykinesia or rigidity during the day.

Our study is not without limitations. Fluctuations of movement can be present in PD during the day, but probably also during the night, and we have not taken this into account. Future studies may also include “off” state assessments, and other measures of motor fluctuations. Cognitive decline may influence sleep quality in itself, but also the reliability of the rating scales used. The clinical interview suggested only small memory problems in a minority of our patients, but we did not perform formal cognitive testing.

In general the first choice treatment of subjectively impaired bed mobility is dopaminergic treatment. Studies show that sleep quality improves after evening doses of slow release levodopa preparations or continuous release dopamine-agonists.[25-30] Moreover post-hoc analysis of these data show a specific improvements on subjective bed mobility.[26] Our results show that, although total LED dose over the day was higher in PD+IBM patients, the dose taken before going to bed was not. As PD+IBM patients also had more progressed disease, the finding that both groups were treated with comparable LED dose at night may suggest a dopaminergic deficit at night for this group. Therefore, our findings suggest the need for increased dopaminergic treatment in PD patients with self-reported IBM.

Our results show that patients with small numbers of body position do not necessary have bad sleep quality, therefore it is questionable if improvement of sleep quality after taking dopaminergic treatment is caused by an actual improvement of body position changes during the night, or only an improvement of the subjective feeling. To get more insight into the working effect of dopaminergics, future research should focus on the influence of the treatment on objective bed mobility, rather than subjective complaints alone. In any case, the dissociation between subjective complaints and objective sleep quality means that a clinical diagnosis of "nocturnal hypokinesia" should be reserved for patients who not only complain about impaired bed mobility but have actual sleep disturbances as well.







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# 4

# Nocturnal movements in the preclinical phase of Parkinson's disease

**Published as**

Accelerometer–based quantitative analysis of axial nocturnal movements differentiates Parkinson's disease patients but not high risk individuals from controls

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## Abstract

### *Introduction*

*There is a need for prodromal markers to diagnose Parkinson's disease (PD) as early as possible. Knowing that most patients with overt PD have abnormal nocturnal movement patterns, we hypothesized that such changes might occur already in non-PD individuals with a potentially high risk for future development of the disease.*

### *Methods*

*Eleven patients with early PD (Hoehn&Yahr stage ≤ 2.5), 13 healthy controls, and 33 subjects with a high risk of developing PD (HR-PD) were investigated. HR-PD was defined by the occurrence of hyperechogenicity of the substantia nigra in combination with prodromal markers (e.g. slight motor signs, olfactory dysfunction). A tri-axial accelerometer was used to quantify nocturnal movements during two nights per study participant. Outcome measurements included mean acceleration, and qualitative axial movement parameters such as duration and speed.*

### *Results*

*Mean acceleration of nocturnal movements was lower in PD patients compared to controls. Frequency and speed of axial movements did not differ between PD patients and controls, but mean size and duration were lower in PD. The HR-PD group did not significantly differ from the control group in any of the parameters analyzed.*

### *Conclusion*

*Compared to controls, PD patients had an overall decreased mean acceleration, as well as smaller and shorter nocturnal axial movements. These changes did not occur in our potential HR-PD individuals, suggesting that relevant axial movement alterations during sleep have either not developed or cannot be detected by the means applied in this at risk cohort.*






## Introduction

The diagnosis of Parkinson's disease (PD) based on the UK Brain bank criteria demands the presence of bradykinesia together with either muscle rigidity, rest tremor or postural instability.[1] Pathological studies have demonstrated that by the time PD diagnosis is made, 40–60% of dopaminergic neurons in the substantia nigra have already degenerated.[2] PD does not only affect motor performance, but also leads to an increased occurrence of non-motor symptoms such as sleep disorders, autonomic dysfunction and alterations of mood. The onset of most of these symptoms antecedes the clinical PD diagnosis.[3] Imaging studies have shown that parts of the substantia nigra are affected 3–7 years prior to clinical diagnosis.[2,4–6] The start of the PD-specific neurodegenerative process may even be years to decades earlier than the characteristic motor symptoms which enable clinical diagnosis of PD. This prodromal phase is associated with an increased probability to have non-motor signs or symptoms (e.g. hyposmia,[7,8] REM sleep behavior disorder,[9–11] depression,[12] constipation[12,13]), and/or slight motor symptoms (e.g. reduced arm swing, trunk instability,[14] stiffness and slowness not sufficient for the diagnosis of PD but increasing the likelihood for its future onset[15–17]), and/or imaging abnormalities (e.g. enlarged hyperechogenic substantia nigra[18–20]). However, the non-motor signs are not specific for PD as they are frequently present in the elderly population or co-occur with other diseases.[21] Based on the limitation of the different markers it seems promising to combine risk markers and clinical symptoms to best predict a PD-related early neurodegenerative process. A promising approach to identify individuals at high risk for PD might be the use of transcranial sonography (TCS). This ultrasound sign (SN+) is prominent in more than 90% of diagnosed PD patients.[18,20] In the elderly population, persons with SN+ assessed by TCS have a 17 fold increased risk of future disease onset within 3 years and 20.6 fold increased risk after 5 years.[22]

Nocturnal movements are clearly altered in PD patients, on the one hand with increased activity levels (e.g. due to rapid eye movement (REM) sleep behavior disorder (RBD) or being awake), and on the other hand a decreased frequency of nocturnal turns.[23–25] These changes may also precede the diagnosis of PD and could therefore be interesting to study as an early PD marker. Based on these earlier findings, we hypothesized that (i) PD patients show different nocturnal movement patterns compared to healthy controls, and (ii) smaller but still detectable differences in nocturnal movements may occur already in non-PD individuals with a potential high risk for future development of the disease (HR-PD) and may thus have the potential to serve as prodromal markers of the disease.

# Methods

## Population and study design

All participants were investigated in the frame of the PMPP study (Progression Markers in the Premotor Phase of Parkinson's disease).[14,26] This study comprises a population of 16 PD patients in early disease stages, 40 individuals supposed to be at high risk for PD (see below) and 14 controls with no risk marker for PD. The aims of the PMPP study are to define (bio-) markers or symptoms which indicate progression into the clinical PD stage, thus allowing an earlier diagnosis. Therefore, the PMPP study focuses particularly on the detection of biomarkers for PD and progression markers in the prodromal phase of PD in individuals selected under the presupposition to be at high risk for developing PD (HR-PD). Recruitment strategy as well as inclusion/exclusion criteria are presented in detail elsewhere.[14,26] In brief, individuals defined as HR-PD had hyperechogenicity of the substantia nigra in addition to concomitant risk or prodromal markers of PD. These subjects had at least one symptom defined as either (a) or (b): (a) one PD cardinal motor sign assessed by the Unified Parkinson's Disease Rating Scale (UPDRS-III) motor part, (b) two of the following prodromal/risk markers: prevalence of depression or history of depression, hyposmia, one-sided reduced arm swing, positive family history of PD.[27-30] All controls had normal echogenicity of the substantia nigra,[31] no signs of acute psychiatric diseases and a negative family history of PD.[30,31] PD patients were defined according the UK Brain Bank criteria and recruited from the outpatient clinic of the Department of Neurodegenerative Diseases, Tübingen, Germany. Inclusion criteria for PD patients were: disease stages ≤ Hoehn&Yahr stage 2.5, age older than 50 years, no deep brain stimulation and no verified genetic mutation known to cause PD.[32] Patients were assessed while taking their optimized antiparkinson medication. The study was approved by the ethical committee of the Medical Faculty of the University of Tübingen, and all individuals provided written informed consent. The participants included in the current study had at least two nocturnal registrations of sleep with an ambulatory device (see below) during the study period.

## Clinical assessment

All participants underwent a thorough clinical examination by neurologists experienced in the field of neurodegenerative disorders. Motor performance was evaluated with the UPDRS motor score (UPDRS-III).[27] Overall dopaminergic treatment was quantified by calculating the Levodopa Equivalent Dose (LED) in mg/day.[33] Subjective sleep quality was measured using the Pittsburg Sleep Quality Index (PSQI).[34] The PSQI assesses different aspects of nocturnal sleep, including sleep latency, duration and efficiency, subjective sleep quality and use of sleep medication. "Poor sleep quality" is defined by a PSQI score of higher than 5. Presence or absence of RBD was assessed with the RBD screening questionnaire (RBDSQ).[35] This scale asks for a subjects' behavior while dreaming, including "dream enacting behavior" and other RBD-associated features. The total score ranges from 0-13 and a score of more than 4 indicates RBD. Presence of restless legs (RLS) was assessed using a questionnaire based on the four cardinal features of RLS.[36] A positive answer to all four features indicates RLS.





## Nocturnal movement assessment

Two nocturnal movement assessments were performed with three orthogonal accelerometers mounted at the back (Dynaport® device, McRoberts, Den Haag, Nederland).[37] The device has a local memory card for data storage. Data are collected at 100 Hz and stored on a secure digital memory card. The tri-axial monitoring provides information on rotations in the longitudinal axis when lying in bed. Night rest is stated as an "in bed period" indicated by longer periods registered as lying. All subjects completed a sleep diary when using the accelerometer, including periods awake during the night. If any discrepancies occurred between sleep times as provided by the sleep diary and sleep time registered by the accelerometer, the registration by the accelerometer was synchronized by the data reported by the patient. The accelerometer gives information on two different aspects of nocturnal movement. First, general aspects of all movements, such as mean acceleration and mean movement time. Second, the device depicts information of axial turns during the night. The characteristics of the axial turns include size, duration and speed. Table 1 shows the different outcome parameters in both categories and their descriptions and units. Furthermore, variation of size, duration and speed of the axial turns during the night were evaluated by calculating the coefficient of variation (standard deviation divided by the mean).

## Data analysis

The first study hypothesis (that PD patients have different movements compared to controls) was tested by comparing nocturnal movements between PD patients and controls. The second hypothesis (that HR-PD subjects already show slight changes in the nocturnal axial movements) was proven by comparing HR-PD individuals to controls. As the quantification of the movement acceleration can be influenced by other variables such as age and motor performance (UPDRS-III), a regression model correcting for these variables was applied. Statistical analyses were done using SPSS for Windows version 18. According to the Kolmogorov-Smirnov test, data were not normally distributed. Therefore, inference statistics and correlation analy-

sis was based on the independent-samples Mann-Whitney-U test and Spearman's rank correlation coefficient. Data are shown as median (range) and N(%) of persons. All results are of two-tailed tests, significance level was set at $p < .05$.

Table 1. Quantitation of nocturnal ambulatory movement parameters

| | |
|---|---|
| In bed period (min) | Total period (in minutes) that the device considers a subject being in bed during the night. |
| General movements | Movements are all periods during the in bed period in which any movement was detected. |
| Mean acceleration (g) | Mean amount of acceleration during all periods of movement during the in bed period. |
| Total acceleration time (%) | Percentage of time during the in bed period that a subject moves. |
| Axial movements | An axial movement is each movement which results in an axial position change of at least 10°. |
| Frequency (movements/h) | Number of axial movements per hour of the in bed period. |
| Size (°) | The angle of the change in position resulting from the axial movement. |
| Duration (s) | Number of seconds the axial movement lasts. |
| Speed (°/s) | Mean size per second of the axial movement. |

## Results

Data of 11 PD patients, 13 controls and 33 HR-PD were analyzed. This yielded 22 nocturnal registrations of PD patients, 26 of controls and 66 of HR-PD. Thus, data of 13 subjects were not included into the data analysis due to technical problems (n=1 HR-PD), poor data quality (n= 2 PD, n=6 HR-PD) or withdrawal from participation in this part of the study (n=3 PD, n=1 control).

### Clinical characteristics and sleep questionnaires

Median disease duration of PD patients was 4.0 years (2.0-10.0). With respect to the antiparkinson medication, the median LED was 447.50 mg/day (100.0-1240.00 mg/day). One patient had a Hoehn&Yahr score of 1, nine of 2, and one of 2.5. As could be expected based on the inclusion criteria, UPDRS-III scores were lower in





controls (UPDRS-III: 0 (0-7)) compared to both the HR-PD subjects (UPDRS-III: 4 (0-12), $p<0.001$) and PD patients (UPDRS-III:18 (7-47), $p < .001$) (Table 2). Based on the sleep questionnaires, nocturnal sleep quality and presence of RBD and RLS were not different among PD and controls and HR-PD and controls (see table 2 for details). However, one person of the control group scored positive for the presence of RBD based on the RBDQ, in the HR-PD and PD group six individuals with RBD according to the scale were identified.

### Nocturnal movements in PD patients and controls

With respect to general movement assessment, mean acceleration was lower in PD patients compared to controls (PD 0.05 g (0.04-0.08) vs. controls 0.08 g (0.05-0.11), $p < .001$). Regression analysis showed that mean acceleration was slightly affected by the motor performance (UPDRS-III, beta -.001, $p = 0.017$) and frequency of turns (frequency beta -.003, $p = .006$). Although, the frequency of axial turns did not significantly differ between both groups, the distribution and quality of the axial turns varied between PD patients and controls. Total size of axial turns was smaller (PD 32.6° (17.5-46.9) vs. controls 46.7° (22.66-73.9), $p < .001$) and duration of turns was shorter (PD 5.7 s (4.07-8.8) vs. controls 7.0 s (5.6-10.2), $p = .001$) in PD patients. Table 3 gives an overview of this data. Variability of axial nocturnal movement performance did not statistically differ between the two study groups ($p>0.162$, see table 3 for details).

### Nocturnal movements in HR-PD and controls

Table 4 shows that mean acceleration of individuals with HR-PD did not significantly differ from controls. Furthermore, no differences were found in the characteristics of axial turns between HR-PD and controls, indicating that nocturnal axial movements are not yet affected in subjects with a high risk of developing PD.

### RBD and nocturnal movements

Although no difference in the prevalence of RBD (18.2% PD, 18.2% HR-PD, 7.7% controls; $p= .443$) was statistically verified, it could not be ruled out that the presence of RBD symptoms modulated the movement profile during the night. Therefore, data were additionally analyzed after exclusion of 9 individuals with RBD (Table 5 and 6). The mean acceleration was significantly lower (PD 0.05 g (0.04-0.08) vs. controls 0.08 g (0.05-0.11), $p < .001$). Furthermore size (PD: 34.5° (17.5-46.9) vs. controls 45.2° (11.7-63.1), $p = .001$) and duration was still shorter (PD 5.8 s (4.1-8.8) vs. controls 7.0 s (5.6-10.2), $p = .002$; Table 4) in PD patients compared to controls. Again, no differences were found between HR-PD patients and controls in any characteristic of nocturnal axial movements (Table 6).

## Association between nocturnal movements and sleep problems

A correlation analysis between the PSQI score and the quantitative movement parameters was performed in order to rule out global effects of poor sleep quality on the alterations in axial nocturnal movements seen in our PD patients. We found no significant correlation between the PSQI score and the calculated movement parameters (mean acceleration = –.155; frequency = .185; size = –.127; duration = –.197; speed = .133, p all > .05).

Table 2. Clinical variables of the three groups

| | Controls | High risk | p1 | PD | p2 |
|---|---|---|---|---|---|
| N patients | 13 | 33 | | 11 | |
| Men (%) | 6 (46.2) | 25 (75.8) | .054 | 7 (63.6) | .392 |
| Age (yr) | 64.0 (56.0–78.0) | 63.0 (55.0–73.0) | .557 | 65.0 (51.0–81.0) | .691 |
| UPDRS III | 0 (0–7) | 4 (0–12) | .001 | 18 (7–47) | **<.001** |
| Sleep questionnaires | | | | | |
| · PSQI | 4 (0–9) | 4 (0–15) | .242 | 5 (1–11) | .134 |
| · PSQI >5 (%) | 2 (15.4) | 13 (39.4) | .118 | 5 (45.5) | .106 |
| · RBDQ | 1 (0–5) | 2 (0–10) | .189 | 2 (1–11) | .252 |
| · RBDQ≥ 5 (%) | 1 (7.7) | 6 (18.2) | .207 | 2 (18.2) | .274 |
| · RLS (%) | 0 (0.0) | 1 (3.0) | .526 | 1 (9.1) | .267 |

*Median (range), p scores based on independent samples Mann–Whitney U test; $p^1$ = p control vs. high risk; $p^2$ = p control vs. PD; UPDRS III = Unified Parkinson's Disease Rating Scale Motor Symptoms, PSQI = Pittsburgh sleep quality index, ESS = Epworth Sleepiness Scale, RBDQ = REM Sleep Behavior Questionnaire, RLS = presence of restless legs syndrome based on the four cardinal symptoms*





Table 3. Movement parameters in PD and controls

| | PD | Controls | p |
|---|---|---|---|
| N participants | 11 | 13 | |
| N registrations | 22 | 26 | |
| In bed period (min) | 399.1 (238.5–725.6) | 458.7 (230.2–596.9) | .185 |
| Mean acceleration (g) | 0.05 (0.04–0.08) | 0.08 (0.05–0.11) | **<.001** |
| Total acceleration time (%) | 1.8 (0.5–13.4) | 1.5 (0.7–4.2) | .148 |
| Total axial movements | | | |
| · Frequency (movements/h) | 5.0 (0.7–17.8) | 3.1 (1.2–8.4) | .148 |
| · Size (°) | 32.6 (17.5–46.9) | 46.7 (22.7–73.9) | **<.001** |
| · Duration (s) | 5.7 (4.1–8.8) | 7.0 (5.6–10.2) | **.001** |
| · Speed (°/s) | 6.8 (4.1–9.4) | 7.4 (4.1–12.7) | .203 |
| Variability of movements | | | |
| · CV size | 0.7 (0.5–1.1) | 0.6 (0.4–0.9) | .475 |
| · CV duration | 0.6 (0.4–0.8) | 0.52 (0.3–0.8) | .162 |
| · CV speed | 0.5 (0.3–1.1) | 0.6 (0.4–0.9) | .259 |

*Median (range), p scores based on independent samples Mann–Whitney U test*
*CV = coefficient of variation*

Table 4. Movement parameters in HR-PD and control

| | HR-PD | Controls | p |
|---|---|---|---|
| N participants | 33 | 13 | |
| N registrations | 66 | 26 | |
| **In bed period (min)** | 458.9 (246.7-623.4) | 458.7 (230.2-596.9) | .927 |
| **Mean acceleration (g)** | 0.07 (0.05-0.12) | 0.08 (0.05-0.11) | .098 |
| **Total acceleration time (%)** | 1.4 (0.4-5.1) | 1.5 (0.7-4.2) | .351 |
| **Total axial movements** | | | |
| · Frequency (movements/h) | 3.0 (0.5-8.6) | 3.1 (1.2-8.4) | .703 |
| · Size (°) | 51.2 (18.8-77.0) | 46.7 (22.7-73.9) | .052 |
| · Duration (s) | 7.8 (3.4-15.6) | 7.0 (5.6-10.2) | .134 |
| · Speed (°/s) | 7.5 (4.2-14.0) | 7.4 (4.1-12.7) | .640 |
| **Variability of movements** | | | |
| · CV size | 0.6 (0.0-1.2) | 0.6 (0.4-0.9) | .456 |
| · CV duration | 0.5 (0.3-0.9) | 0.5 (0.3-0.8) | .278 |
| · CV speed | 0.6 (0.4-1.3) | 0.6 (0.4-0.9) | .775 |

*Median (range), p scores based on independent samples Mann-Whitney U test*
*CV = coefficient of variation*





Table 5. Movement parameters PD and control

| | PD | Controls | p |
|---|---|---|---|
| N participants | 9 | 12 | |
| N registrations | 18 | 24 | |
| **In bed time (min)** | 392.4 (238.5-513.3) | 462.6 (230.2-596.9) | .064 |
| **Mean acceleration (g)** | 0.05 (0.04-0.08) | 0.08 (0.05-0.11) | **<.001** |
| **Total acceleration time (%)** | 1.8 (0.5-13.4) | 1.6 (0.7-4.2) | .213 |
| **Total axial movements** | | | |
| · Frequency (movements/h) | 4.6 (0.7-17.8) | 2.9 (1.2-8.4) | .374 |
| · Size (°) | 34.5 (17.5-46.9) | 45.2 (11.7-63.1) | **.001** |
| · Duration (s) | 5.8 (4.1-8.8) | 7.0 (5.6-10.2) | **.002** |
| · Speed (°/s) | 6.8 (4.1-9.4) | 7.1 (4.1-10.2) | .550 |
| **Variability of movements** | | | |
| · CV size | 0.6 (0.5-1.0) | 0.7 (0.4-0.9) | .517 |
| · CV duration | 0.5 (0.4-0.8) | 0.6 (0.3-0.8) | .731 |
| · CV speed | 0.6 (0.3-1.1) | 0.6 (0.4-0.9) | .182 |

*Median (range), p scores based on independent samples Mann-Whitney U test*
*CV = coefficient of variation*

Table 6. Movement parameters in HR-PD and control

| | HR-PD | Controls | p |
|---|---|---|---|
| N participants | 27 | 12 | |
| N registrations | 54 | 24 | |
| In bed time (min) | 460.1 (246.7-623.4) | 462.6 (230.2-596.9) | .983 |
| Mean acceleration (g) | 0.07 (0.05-0.10) | 0.08 (0.05-0.11) | .134 |
| Total acceleration time (%) | 1.5 (0.7-5.1) | 1.6 (0.7-4.2) | .527 |
| Total axial movements | | | |
| · Frequency (movements/h) | 3.1 (1.3-8.6) | 2.9 (1.2-8.4) | .845 |
| · Size (°) | 50.4 (33.5-77.0) | 45.2 (11.7-63.1) | **.021** |
| · Duration (s) | 7.8 (4.4-15.6) | 7.0 (5.6-10.2) | .221 |
| · Speed (°/s) | 7.5 (4.2-14.0) | 7.1 (4.1-10.2) | .488 |
| Variability of movements | | | |
| · CV size | 0.6 (0.4-1.2) | 0.7 (0.5-0.9) | .369 |
| · CV duration | 0.5 (0.3-0.8) | 0.6 (0.3-0.8) | .127 |
| · CV speed | 0.6 (0.4-1.3) | 0.6 (0.4-0.9) | .745 |

*Median (range), p scores based on independent samples Mann-Whitney U test*
*CV = coefficient of variation*

## Discussion

The aim of this study was to examine axial nocturnal movements in early PD stages and in the prodromal phase of PD, hypothesizing that PD patients might show different axial nocturnal movement patterns compared to healthy controls. Moreover, we speculated that these abnormalities might even be prominent in the prodromal phase of PD and may thus have the potential to serve as preclinical markers of the disease. Our results suggest that mean acceleration, size and duration of axial movements are especially altered in the overt motor phase of PD, but not in our individuals suggested to be at high risk for the development of PD.





### Nocturnal movement alteration in overt PD

In our PD sample, we identified a decrease in mean acceleration during the night. Looking at the characteristics of the axial turns, PD patients made smaller turns, in shorter time periods. A lower frequency of turning-over events in bed in PD patients was reported by Laihinen and colleagues, however we could not support this.[25] In contrast, elevated nocturnal activity level and an increased proportion of time with movement have been reported in PD as well.[23,24] The latter findings are based on the quantification of an activity level. This elevated activity level might be influenced partly by movements occurring in prolonged periods in which patients are awake during the night. This might also be a problem in our results. Bedtime was measured as a longer period of lying, however this does not directly indicate a person is asleep. Using the sleep diaries of the patients, we narrowed this period based on the patients' experience of being asleep. We believe this combination of factors gives a good comprehension of actual sleep, however future studies may overcome this issue by use of polysomnography.

During the day, an increase of variation in (gait) movements has been described in both PD patients and in a genetically defined PD at risk cohort.[38,39] Our data suggests that the variability of axial movements is not altered during the night in PD patients. An explanation of this could be that PD related neurodegeneration mostly affects voluntary day time movements rather than the involuntary movements during the night. However, further research is needed to verify this finding.

In general, our data suggest that PD patients may attempt to turn, but are not able to reach the full size of movements. Although size and duration of movements were altered in the PD group, the speed level of movements was similar to that of healthy controls. From this finding one could speculate that PD-related axial motor dysfunction during the night influences the size of the movements rather than its speed.

### Nocturnal movement alteration in the prodromal stage of PD

There are currently several ongoing studies attempting to identify PD biomarkers, although further identification of these markers is necessary.[21] To date, several non-motor and motor risk factors have been reported to increase the risk for later development of PD, especially presence of RBD.[15,16,40] In our sample, frequency of RBD did not differ between the PD and HR-PD group, suggesting that frequency of RBD in our HR-PD cohort resembles that in PD. As we expected that RBD symptoms might affect the interpretation of our nocturnal axial movement data, analysis was replicated after exclusion of all subjects with signs of RBD. Our analysis revealed,

independent from the presence of RBD, that frequency, speed, duration and intensity of axial nocturnal movements were not altered in our HR–PD sample compared to controls. This leads to the conclusion that occurrence of RBD did not relevantly influence our general finding that axial nocturnal movements are different between PD and controls.

As this is a cross–sectional study, we cannot "guarantee" that our HR–PD group indeed reflects a prodromal PD stage. However, we recently identified subtle signs of a balance deficit (i.e. increased variability of trunk acceleration) in this group, especially under challenging conditions.[14,38] In our view, this argues in favor of the hypothesis that our HR–PD cohort indeed bears an increased risk for the development of PD. However, only longitudinal assessments will clarify how many persons of this group will develop PD in the near future. Imaging data monitoring abnormalities of the striatal dopaminergic systems are also helpful to identify persons among the HR–PD group already showing an ongoing PD related neurodegenerative process.

In our study we included two registrations of sleep of each participant. Since this was the first study to use movements patterns instead of total activity no data exist on the optimal amount of registrations preferred. A recent study using the same device showed that for daytime position changes the amount of three registration days was sufficient.[41] We believe that variance in night activity is smaller than that of daytime activity, therefore a registration of two nights seems adequate. The large standard deviation in some of the parameters was mainly caused by variation in movements between patients, rather than variation within two nights of the same patients. Analysis showed that the range with respect to frequency the standard deviation between two nights in the same participant was below 2.0 for 90% of the participants. Further research should indicate the optimal amount of registrations needed.

## Conclusion

Despite dopaminergic treatment, PD patients have problems in axial nocturnal movements, even in early stages of the diseases. This may at least partly trigger alterations in sleep patterns which frequently occur during the disease process. Our results did not show any differences in nocturnal axial movements between HR–PD and controls, indicating that this sign is not prominent in our individuals suggested to be at high risk for the development of PD. However, only longitudinal assessments will clarify how many persons of this group will develop PD in the future.





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# Actigraphy
## as a diagnostic tool in REM sleep behavior disorder

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Actigraphy as a diagnostic aid for REM sleep behavior disorder in Parkinson's disease

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## Abstract

### *Background*

*Rapid eye movement (REM) sleep behavior disorder (RBD) is a common parasomnia in Parkinson's disease (PD) patients. The current International Classification of Sleep Disorders (ICSD–II) requires a clinical interview combined with video polysomnography (video–PSG) to diagnose. The latter is time consuming and expensive and not always feasible in clinical practice. Here we studied the use of actigraphy as a diagnostic tool for RBD in PD patients.*

### *Methods*

*We studied 45 consecutive PD patients (66.7% men) with and without complaints of RBD. All patients underwent one night of video–PSG and eight consecutive nights of actigraphy. Based on previous studies, the main outcome measure was the total number of bouts classified as "wake", compared between patients with (PD+RBD) and without RBD (PD– RBD).*

### *Results*

*Twenty–three (51.1%) patients had RBD according to the ICSD–II criteria. The total number of wake bouts was significantly higher in RBD patients (PD+RBD 73.2±40.2 vs. PD–RBD 48.4±23.3, p = .016). A cut off of 95 wake bouts per night resulted in a specificity of 95.5%, a sensitivity of 20.1% and a positive predictive value of 85.7. Seven patients were suspected of RBD based on the interview alone, but not confirmed on PSG; six of whom scored below 95 wake bouts per night on actigraphy.*

### *Discussion*

*PD patients with RBD showed a significantly higher number of bouts scored as "wake" using actigraphy, compared to patients without RBD. In clinical practice, actigraphy has a high specificity, but low sensitivity in the diagnosis of RBD. The combination of actigraphy and previously reported RBD questionnaires may be a promising method to diagnose RBD in patients with PD.*






## Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia that occurs frequently in patients with Parkinson's disease (PD), with an estimated prevalence of 30–60%.[1–3] RBD is characterized by the enactment of dreams as a result of the loss of physiological atonia during REM sleep. Behaviors displayed include hitting, kicking, shouting but also laughing. The associated dreams are often violent or frightening in origin, and sometimes patients harm themselves or their bed partners with their movements.[1] Remarkably, the RBD–associated movements of PD patients are usually much faster, stronger and smoother than during the day, suggesting that the movements "bypass" the affected extrapyramidal systems.[4]

To make a diagnosis of RBD, the current 2nd edition of the International Classification of Sleep Disorders (ICSD–II) requires the combination of clinical features (either by history or on nocturnal video recordings) and the presence of REM sleep without atonia as an electromyographic (EMG) finding during sleep recordings (Table 1).[5] The gold standard for the diagnosis of RBD therefore entails a clinical interview, preferably by a sleep medicine specialist, together with at least one night of polysomnography with audiovisual recordings (video–PSG). However, referring every PD patient with complaints of nocturnal restlessness to a sleep medicine center is time–consuming, expensive and may not always be feasible in clinical practice. As a result, many movement disorder specialists base their diagnosis of RBD solely on the description of the typical behaviors by the bed partner of the patient. Studies show that this practice results in frequent misdiagnoses and, consequently, overtreatment.[6] Mimicking disorders such as obstructive sleep apnea, confusional arousals and nocturnal hallucinations should be excluded, especially because some of these may worsen with clonazepam, the first–line treatment of RBD.[7] Therefore, there is a need for less expensive, easy to use methods to diagnose RBD.

The REM sleep behavior disorder screening questionnaire (RBDSQ) was developed as an easy to use screening method.[8,9] The scale was created in German and English and more recently a Japanese version has been validated.[10] Although the questionnaire shows good internal consistency and a high sensitivity (96%) compared to the clinical interview, it has a low specificity (56%).[8] The REM sleep behavior disorder questionnaire Hong Kong (RBDQ–HK) has been developed, tested and validated in Chinese patients based on the ICSD–II criteria.[11] It was validated in a group of PSG–confirmed RBD patients and controls. The overall RBDQ–HK score was significantly higher in the RBD group. ROC analysis showed that a cut off score of 18/19

had moderate sensitivity and specificity.[11] More recently Frauscher et al. published a validation study of the Innsbruck REM sleep behavior disorders inventory.[12] The scale had a sensitivity of 91.4% and a specificity of 85.7% for both idiopathic and PD related RBD (AUC, 0.886). Interestingly, the scores of patients sleeping alone were comparable with patients with a bed partner.

**Table 1.** ICSD-II criteria for REM sleep behavior disorder[5]

**Presence of REM sleep without atonia**

The EMG finding of excessive amounts of sustained or intermittent elevation of submental EMG tone or excessive phasic submental or (upper or lower) limb EMG twitching.

**At least one of the following is present:**

- Sleep related injurious, or disruptive behaviors by history
- Abnormal REM sleep behaviors documented during PSG monitoring
- Absence of EEG epileptiform activity during REM sleep unless RBD can be clearly distinguished from any concurrent REM sleep-related seizure disorder.
- The sleep disturbance is not better explained by any other sleep disorder, medical or neurological disorders, mental disorders, medication use, or substance abuse

*EMG = electromyography , EEG= electroencephalography , PSG= polysomnography, RBD = REM sleep behavior disorder, REM = Rapid eye movement*

Actigraphy has been suggested as another possible diagnostic tool for RBD. Actigraphy may be a useful instrument to obtain general measures such as total sleep time, sleep efficiency and wake after sleep onset.[13,14] Compared to questionnaires, actigraphy should give a more objective representation of actual motor activity during the night. In addition, actigraphy is much less expensive and cumbersome compared to video-PSG and could be used in a home setting for several days, which may compensate for night-to-night fluctuations in the presence or severity of RBD symptoms. As such the use of actigraphy in the diagnosis of RBD seems attractive and the first results on its use are indeed promising. Naismith et al. found that PD patients with RBD had a higher number of bouts scored as "wake" by actigraphy, compared to patients without RBD, based on questionnaires.[15] In the current study, we sought to confirm these findings in a larger group of well-defined PD patients. We compared actigraphy outcomes in PD patients with and without RBD, based on the gold standard of a clinical interview in combination with video-PSG. Furthermore we searched for an optimal cut-off point to actually implement the use of actigraphy in clinical practice.





# Patients and methods

## Design and study population

All patients were recruited from Sleep Medicine Center Kempenhaeghe, a tertiary clinic for patients with sleep disorders in the Netherlands. At Kempenhaeghe, PD patients with sleep complaints are seen in a dedicated program, including an extensive clinical consultation followed by attended video-PSG that night. Referral reasons could be diverse e.g. insomnia, restless legs syndrome, sleep apnea, and thus did not only pertain to RBD. We included all consecutive idiopathic PD patients referred to the clinic as part of their regular care. All patients satisfied the UK Brain bank criteria for PD and were assessed using their usual medication. Data were collected as part of the regular medical care. The study was performed according to the guidelines of the Medical Ethical Committee of the Radboud University Nijmegen Medical Center. All patients gave informed consent to use these data for further study.

## Clinical characteristics

Demographic, clinical and disease characteristics were recorded. Disease stage was rated using the Hoehn&Yahr staging system.[16] The use of levodopa mono therapy, dopamine agonist mono therapy and combination therapies was registered. Overall dopaminergic treatment was quantified by calculating the Levodopa Equivalent Dose (LED) in mg/day.[17] In addition, nocturnal dopaminergic treatment was estimated by the dopaminergic dose taken before going to bed in LED (LED-night). The use of anti-depressants -which can cause or aggravate RBD- was actively asked for and listed.

## RBD diagnosis

The diagnosis of RBD was made according to the ICSD-II criteria. During the clinical interview, the presence of movements and vocalizations during sleep was screened for by a sleep specialist experienced with PD (ML and SO). The interview was followed by one night of video-PSG. Sleep was scored by laboratory technicians highly experienced with scoring polysomnographic recordings in PD patients, and checked by a sleep medicine specialist (SO). The presence of REM sleep without atonia was determined by quantifying the EMG-signal of the m. submentalis using the "SinBar-group" criteria.[18] Tonic EMG activity was scored in 30 seconds epochs and was considered pathological if the amplitude was more than twice the background amplitude or exceeded 10 μV in more than 50% of the epoch. Phasic EMG activity was scored in 3 seconds mini-epochs and determined to be increased when it contained a burst of EMG activity lasting between 0.1 and 5.0 seconds with an amplitude ex-

ceeding twice the background activity. REM sleep without atonia was diagnosed when more than 18% of 3 second mini-epochs of REM sleep contained increased tonic and/or phasic EMG activity.[18] Finally, the presence of abnormal REM sleep behaviors during PSG was determined using the synchronized video recordings.

### Actigraphy

Actigraphy was performed using the Actiwatch system (Actiwatch AW4, Cambridge Neurotechnology Ltd, Cambridgeshire, United Kingdom), a piezoresistive uni-axial accelerometer. In agreement with previous studies, the recording device was placed on the wrist of the least affected site. Accelerometer signals were digitally sampled at a rate of 32 Hz. The actigraphy device is small, comfortable to wear and according to the patients did not interfere with their normal sleeping behavior. The first night of measurement was done simultaneously with the clinical PSG recording. Sleep and wake times were synchronized with PSG "lights off" and "lights on". After the first night in the sleep center the actigraph was worn for seven consecutive nights at home. Actigraphy data were analyzed using Sleep Analysis 7.23 software (Cambridge Neurotechnology Ltd, Cambridgeshire, United Kingdom). Epoch length was set on 0.25 min. Outcome measurements were total sleep time, sleep efficiency, sleep latency, number and length of wake bouts and total and mean activity scores. Wake bouts during the sleep interval were defined as the total number of continuous blocks in an interval where the activity within the epoch was above the sleep threshold and therefore scored as "wake". The wake threshold value (i.e. the number of activity counts used to define wake) was set to medium sensitivity, i.e. 40.0 activity counts per epoch.

### Data analysis

Actigraphic measurements were compared between PD patients with and without the diagnosis of RBD. Comparisons were tested using independent t-test and chi-square test depending on the variable. As the Hoehn&Yahr stage was not normally distributed, a Mann- Whitney U test was used for this variable. Using Pearson's correlation coefficients, associations were analyzed between the number of bouts classified as wake by actigraphy and actual wake time during the PSG recording. Multiple regression analysis was used to correct for actual wake time according to the PSG in the estimation of the number of bouts classified as wake by actigraphy. The diagnostic accuracy of the number of wake bouts as a diagnostic tool for the presence of RBD, was assessed using ROC analyses. Sensitivity, specificity and positive predictive value were calculated. Missing values were <5%, therefore all percentages are presented as valid percentages. All data are shown as mean±SD or N (%). All results are based on two-tailed tests, with a significance level set at $p < .05$.





## Results

### Study population

During the study period, 54 PD patients were included. Nine patients were excluded from the analysis, one because of technical problems and eight because they had less than 10 minutes of REM sleep during the PSG. Twenty-three of the 45 remaining patients (51.1%) were diagnosed with RBD according to the ICSD-II criteria.

Table 2. Clinical and disease characteristics

| | PD+RBD | PD-RBD | p |
|---|---|---|---|
| N | 23 | 22 | |
| Men (%) | 17 (73.9) | 13 (59.1) | .292 |
| Age (yr) | 64.3±9.4 | 58.1±8.8 | **.028** |
| Disease duration (yr) | 9.5±6.4 | 4.3±2.8 | **.024** |
| LED (mg/day) | 1089.4±582.9 | 697.7±563.1 | **.027** |
| LED night (mg/day) | 117.2±51.8 | 140.6±40.9 | .298 |
| Hoehn&Yahr (%) | | | **.025** |
| 1 | - | 2 (9.1) | |
| 1.5 | - | 4 (18.2) | |
| 2 | 16 (69.6) | 13 (59.1) | |
| 2.5 | 4 (17.4) | - | |
| 3 | 3 (13.0) | 3 (13.6) | |
| Use of anti-depressants | | | |
| · SSRI (%) | 4 (17.4) | 4 (18.2) | .945 |
| · TCA (%) | - | 2 (9.1) | .139 |
| · Other (%) | 3 (13.0) | - | .080 |

*Results are mean±SD, except if otherwise specified; LED Levodopa Equivalent Dose; LED night Levodopa Equivalent Dose taken before going to bed; SSRI Selective Serotonin Reuptake Inhibitors; TCA Tricyclic Antidepressants*

## Clinical and disease characteristics

In table 2, clinical demographic as well as disease characteristics of the study subjects are summarized. Patients with RBD (PD+RBD) were older than those without (PD−RBD). Disease severity was higher in patients with RBD with longer disease duration and more advanced H&Y disease stage (Table 2). PD+RBD patients used higher doses of dopaminergic treatment. In the PD+RBD group ten patients used levodopa only and thirteen patients used a combination of levodopa and a dopamine agonist. Three patients in the PD−RBD group did not use medication, three were on levodopa monotherapy, four on dopamine agonist monotherapy, and twelve used a combination of levodopa and a dopamine agonist. Use of anti−depressants was not different between groups.

## Sleep parameters

Objective sleep quality in PD+RBD patients was lower; patients with RBD spent more time awake, and had a shorter total sleep time and lower sleep efficiency (Table 3). The prevalence of sleep disorders other than RBD was not different between groups (Table 3).

## Actigraphy

Actigraphy results are presented in Table 4, both during the first night (i.e. simultaneous with the video−PSG) and for the eight consecutive nights in total. In contrast to the PSG results, total sleep time and sleep efficiency as estimated by actigraphy were not different between patients with and without PD, both during the first night and overall eight nights. The total number of bouts classified as wake was 30% higher in the PD+RBD compared to PD−RBD group (PD+RBD 73.2±40.2 vs. PD−RBD 48.4±23.3, p = .016). This was not the case for the length of the wake bouts. Total activity and mean activity scores during sleep were not different either. As several clinical characteristics differed between patients with and without PD, comparisons were repeated using multiple regression analyses correct for these variables, however this did not change the results. Although a correlation was found between number of bouts classified as wake and actual wake time (r = .31, p = .039), regression analysis correcting for actual wake time still showed a significant effect of the presence of RBD on the number of wake bouts (R−squared = 0.18, standardized−beta = 0.31, p = .043).

## Actigraphy in clinical practice

To study the clinical relevance of the previous findings, we calculated the sensitivity, specificity and the positive and negative predictive value of actigraphy for the diagnosis of RBD. Figure 1 shows the distribution of wake bouts in the PD+RBD and





Table 3. Sleep parameters

| | PD+RBD | PD−RBD | p |
|---|---|---|---|
| N | 23 | 22 | |
| **PSG results** | | | |
| · Total sleep time (min) | 330.0±51.6 | 375.6±65.9 | **.008** |
| · Sleep efficiency (%) | 67.9±8.7 | 76.3±10.7 | **.004** |
| · Sleep latency (min) | 13.8±12.2 | 10.1±8.1 | .138 |
| · % N1 | 15.2±8.0 | 10.3±5.2 | **.037** |
| · % N2 | 58.9±11.3 | 58.0±10.9 | .677 |
| · % N3 | 13.0±11.3 | 15.7±9.5 | .304 |
| · % REM | 13.0±8.3 | 15.9±7.2 | .118 |
| · % Wake | 30.0±9.4 | 22.6±10.9 | **.003** |
| · Awakenings (no.) | 35.3±14.5 | 28.9±11.1 | .109 |
| · PLM index | 36.2±47.2 | 21.7±31.9 | .138 |
| **Other sleep diagnoses** | | | |
| · Insomnia (%) | 18 (78.3) | 18 (81.8) | .766 |
| · OSAS (%) | 6 (26.1) | 9 (40.9) | .292 |
| · RLS (%) | 6 (26.1) | 6 (27.3) | .928 |
| · Hypersomnia (%) | 12 (52.2) | 8 (36.4) | .286 |

*Results are mean±SD, except if otherwise specified*

*% N1 (N2, N3, REM) = percentage in stage N1 (N2, N3, REM) sleep), PLM = periodic limb movement OSAS = obstructive sleep apnea syndrome, RLS = restless legs syndrome*

PD−RBD groups. A cut−off of 95 wake bouts per night yielded a specificity of 95.5%, a sensitivity of 26.1%, a positive predictive value of 85.7% and a negative predictive value of 55.3%. Figure 2 shows the ROC curve when using different cut−offs for the number of wake bouts during the eight measurement nights. The area under the curve was 0.696 with a significance of p = .025. Figure 3 shows the resulting positive and negative predictive values according to different prevalence rates of RBD; which in our cohort was 51.1%.

We additionally looked at the final diagnosis for patients where the clinical interview was incongruent with the final diagnosis of RBD. Based on the clinical interview, seven patients were suspected of having RBD, but did not fulfill the full ICSD−II criteria.

Table 4. Actigraphy results

| | PD+RBD | PD−RBD | p |
|---|---|---|---|
| N | 23 | 22 | |
| **Actigraphy night 1** | | | |
| · Total sleep time (min) | 396.5±72.0 | 429.1±58.4 | .103 |
| · Sleep efficiency | 82.7±12.3 | 87.6±8.7 | .133 |
| · Sleep latency (min) | 3.3±6.5 | 2.4±4.7 | .580 |
| · No wake bouts | 78.4±46.1 | 49.5±22.2 | **.011** |
| · Length wake bouts (min) | 1.1±0.5 | 1.2±0.6 | .488 |
| · Total activity score | 12943.8±11432.2 | 10132.6±6847.6 | .325 |
| · Mean activity score | 6.9±5.7 | 5.4±3.9 | .299 |
| **Actigraphy mean of 8 nights** | | | |
| · Total sleep time (min) | 397.4±91.1 | 389.5±64.1 | .738 |
| · Sleep efficiency | 78.4±14.6 | 84.7±9.5 | .097 |
| · Sleep latency (min) | 10.0±10.6 | 5.8±10.3 | .187 |
| · No wake bouts | 73.2±40.2 | 48.4±23.3 | **.016** |
| · Length wake bouts (min) | 1.3±0.6 | 1.4±0.5 | .689 |
| · Total activity score | 17885.2±14375.8 | 12613.9±9793.2 | .160 |
| · Mean activity score | 10.4±11.5 | 7.2±5.4 | .231 |

*Results are mean±SD*

All but one of these patients had sleep initiation or maintenance problems (insomnia); two were diagnosed with obstructive sleep apnea syndrome, two had restless legs syndrome, three showed an increased level of periodic leg movements, and one suffered from nocturnal hallucinations (Table 5). Six of the patients had a wake bout count lower 95 (Table 5). Seven patients did not have a clinical history of RBD, but PSG findings allowed an RBD diagnosis according to the ICSD–II criteria. In these patients there was either no bed partner, or the bed partner claimed to be always fast asleep not noticing any abnormal behavior of the patient. Additional sleep diagnoses in this group are listed in Table 5. The actigraphy–based number of wake bouts in this group was highly diverse, showing no consistent direction.



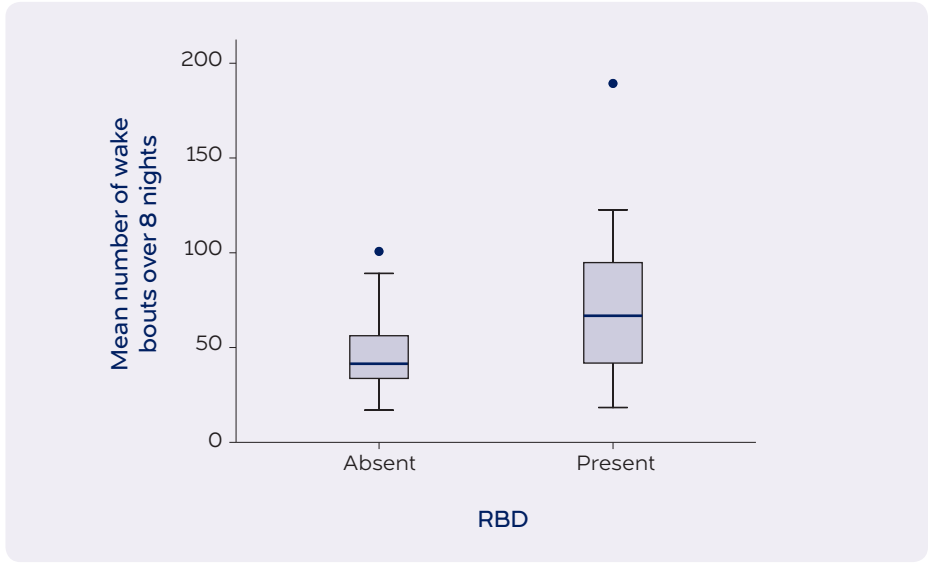


Table 5. Mismatch between RBD diagnosis based on clinical interview and ICSD II criteria

| PD patients with clinical interview suspicious for RBD but not confirmed by ICSD II criteria | | |
|---|---|---|
| Study number | Final diagnoses | Number of wake bouts according to actigraphy |
| 21 | OSAS | 52.4 |
| 24 | Insomnia, PLMD | 100.7 |
| 29 | Insomnia, PLMD, hallucinations | 19.4 |
| 32 | Insomnia, RLS | 56.3 |
| 48 | Insomnia | 28.0 |
| 71 | Insomnia, RLS, PLMD | 83.5 |
| 73 | Insomnia, OSAS | 42.1 |
| **PD patients with clinical interview negative for RBD but with diagnosis based on ICSD II criteria** | | |
| Study number | Other diagnoses next to RBD | Number of wake bouts according to actigraphy |
| 1 | Insomnia, OSAS, RLS | 108.1 |
| 12 | Insomnia, RLS, PLMD | 92.3 |
| 16 | Insomnia | 59.8 |
| 44 | Insomnia | 25.7 |
| 45 | Insomnia, RLS, PLMD | 189.3 |
| 65 | Insomnia, RLS | 32.9 |
| 75 | Insomnia, PLMD | 71.5 |

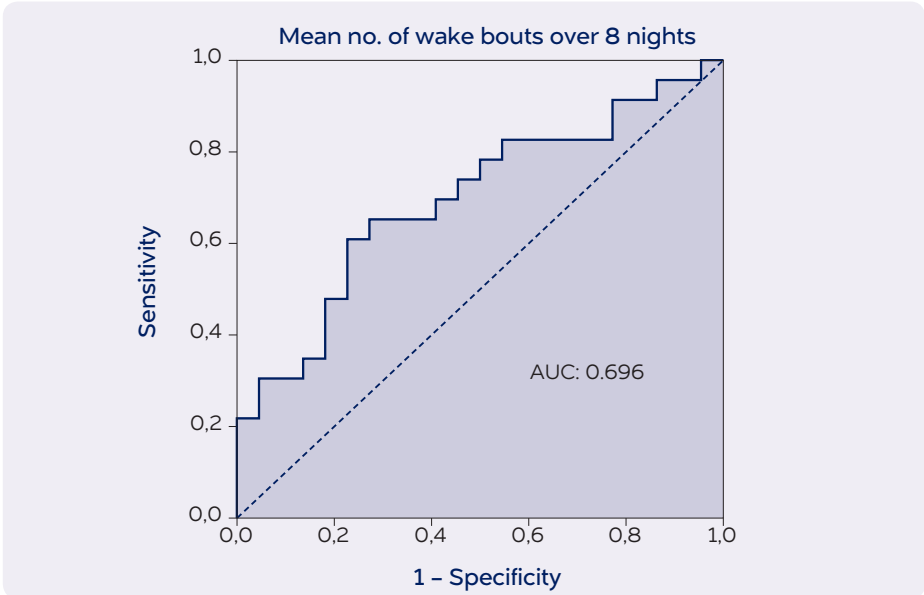
*OSAS = obstructive sleep apnea syndrome; PLMD = periodic leg movement disorder; RLS = restless legs syndrome*

Figure 1. Distribution of wake bouts in PD+RBD and PD−RBD




*Boxplot of number of wake bouts per night measured over 8 nights in PD+RBD and PD−RBD*

Figure 2. ROC curve number of wake bouts

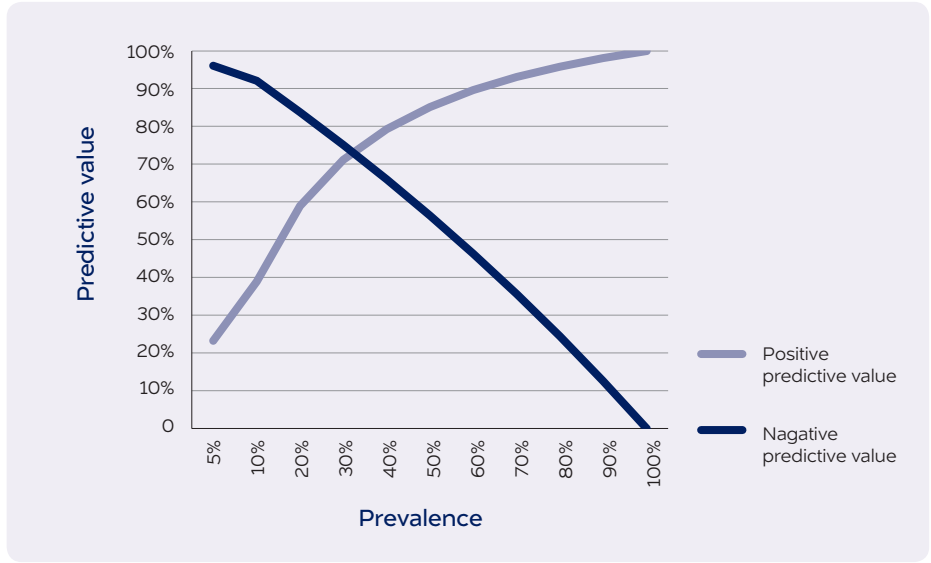



*Number of wake bouts measured over 8 nights; Area under the curve (AUC) = 0.696*





Figure 3. Prevalence and predictive value




# Discussion

Solely using the clinical interview to assess the possible presence of RBD in PD patients, often results in misdiagnoses. However, even judicious use of video−PSG is costly and not always feasible. Therefore, there is a clear need for new screening tools for RBD. Our results show that using actigraphy, the number of bouts classified as “wake” is significantly higher in PD patient with RBD compared to PD patients without. Accordingly, we show that actigraphy has a very high specificity and a good positive predictive value for diagnosing RBD in PD patients.

Wake bouts as scored by actigraphy were previously suggested as a possible useful marker in the diagnostic workup of RBD in PD: our findings are in agreement with Naismith et al., who studied 22 patients with 14 consecutive nights of actigraphy.[15] However, the actual number of wake bouts was almost twice as high in our patient group, compared to theirs. Since sensitivity settings of the actigraphs were the same, this difference may have been caused by different epoch length settings, which was 0.25 min in our study and 0.50 in the study of Naismith et al..[15] In addition, we used video−PSG in combination with a clinical interview by a sleep medicine specialist as the gold standard for the diagnosis of RBD, instead of questionnaires.

Previous studies have suggested that actigraphy is an useful method to measure sleep quality in PD patients. Correlations were found between actigraphy and total sleep time, wake after sleep onset and subjective complaints about nocturnal sleep.[13,14] Our results however showed a difference between total sleep time and sleep efficiency measured with actigraphy and PSG. Although the actigraph was measured on the least affect side, we cannot exclude that the presence of tremor, on–off fluctuations and/or dyskinesias may have influenced the results. More research is needed to study the influence of PD motors symptoms on actigraphic results during the night.

There was no increase in either total or mean activity levels during sleep, which could have been expected in patients with REM related movements. However, as RBD associated movements lead to activity well above the threshold that is represented as "sleep" by actigraphy, they are almost always scored as "wake bouts" rather than increased activity during sleep. Variables other than the presence of RBD may have influenced the number of bouts classified as wake. The periodic limb movement index was, although not significantly, higher in the PD+RBD group compared to the PD–RBD group. The lack of significance could be caused by a large difference in variance. Periodic limb movements can cause sleep disturbances and therefore increase the number of wake bouts. Our groups were not matched with respect to age, disease duration, disease stage and medication use, and these factors may also influence sleep. However, regression analyses correcting for these clinical characteristics and PSG–determined actual wake time during the night, still showed a significant differences in the number of wake bouts between groups. These findings suggest that the increased number of wake bouts is primarily the result of the presence of RBD.

Results showed that using an epoch length of 0.25 min and a cut–off of 95 wake bouts per night, actigraphy is a highly specific tool for RBD in PD patients, albeit with a low sensitivity. As the prevalence of RBD in PD ranges between 30% and 60%, actigraphy has a positive predictive value between 70 and 90% which is reasonable.[1–3] Based on a semi–structured clinical interview alone, we found seven patients incorrectly suspected of having RBD. Of these, only one patient scored above the threshold of 95 wake bouts per night. Therefore, these results show an additional value of using actigraphy next to a clinical interview in the diagnostic trajectory of RBD. Seven patients had no clinical history of RBD–like behavior but still fulfilled the diagnostic PSG criteria of RBD, and actigraphy did not differentiate these patients from the group without RBD. Actigraphy therefore mainly has a role in combination with at least a clinical suspicion of RBD, rather than a screening instrument in PD patients without complaints of RBD. Actigraphy should not be used in the diagnosis





of idiopathic RBD: although clear studies about the prevalence of RBD in the general elderly population are lacking, rates are estimated between 0.38% and 0.50%, leading to a positive predictive value below 5%.[19,20]

Contrary to the high specificity and low sensitivity of actigraphy, previous research showed that RBD questionnaires have a high sensitivity and a somewhat low specificity.[8,10–12] Combining actigraphy and RBD questionnaires could therefore lead to a more accurate diagnosis of RBD. The combination of these two tools could reduce the need for video–PSG even more. Future research should focus on the clinical value of using a combination of both methods.

Our study used the ICSD–II criteria for the diagnosis of RBD. These criteria are not unambiguous unfortunately. They include presence of atonia during REM sleep, which represents a pathological increase of either phasic EMG activity, tonic EMG activity or both. Cut–off points to diagnose pathological increased phasic and tonic EMG activity are not mentioned in the criteria however, and no agreement has been reached on this point among international research groups. Here, we therefore adopted the criteria developed by the SinBar group, although several other visual and computerized scoring methods have been mentioned in literature.[2,18,21–26]



## Conclusion

PD patients with RBD showed a significantly higher number of bouts scored as "wake" using actigraphy, compared to patients without RBD. In clinical practice, actigraphy has a high specificity, but low sensitivity in the diagnosis of RBD. According to our results and previous studies on the use of RBD questionnaires, the combination of both tools could be a promising method to diagnose RBD in PD patients, leading to a decrease in the need for the costly and time–consuming video–PSG.

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# Summary, general discussion

## and future perspectives

*I first present the main findings of the various original studies, and then place these findings within an overarching context.*





## Sleep and sleep disorders in Parkinson's disease

In **Chapter 2.1** we describe that sleep disorders are not only common but also very diverse: often more than one sleep problem is present in a patient with PD. This could lead to difficulties in the recognition and separation of sleep disorders being present. Especially since consultation time is usually short in clinical practice and multiple other PD-related problems should also be discussed. For a neurologist not having much experience with sleep disorders, there is a considerable risk of under-recognition and undertreatment of these problems. Sleep however matters much to the PD patient. In **Chapter 2.2** we studied the importance of sleep compared to other symptoms and daily limits for the PD patient by using a priority list. Seventy percent of the 153 PD patients had disturbed sleep. About a third of them (37.9%) prioritized sleep as an item they wanted to discuss during their visit to the movement disorder specialist. Sleep was the 6th item on the list of 23 potential items. Patients who prioritized sleep had significantly worse sleep quality (PSQI 9.3±3.8 vs. 5.5±2.8, $p < 0.001$), however, patients who prioritized sleep had exactly the same Epworth Sleepiness Scale scores as patients who did not (both 8.0±5.2, $p = .996$). This could indicate that daytime sleepiness is a less important issue than other sleep-related phenomena.

These results show that sleep is an important issue for PD patients and that presence of poor sleep quality is a reason to ask for medical attention. Interestingly, not all patients with poor sleep quality marked sleep as an item on their priority list to discuss with their physician. One explanation is that patients do not always recognize their sleep as being poor. They may not always be aware that their sleep disturbance is related to their PD, and importantly, they may not realize that possible treatment options exists. Another possible explanation is that, although sleep is disturbed, other issues are more important at the time of consultation. Therefore patients do not include sleep among the five most important issues to discuss with their physician. This theory is supported by the fact that patients with the poorest sleep quality (PSQI >10) did prioritize sleep. Excessive daytime sleepiness (EDS) alone was no reason to prioritize sleep for the majority of patients. Next to the other explanations, this could also be caused by the fact that patients, do not perceive their EDS as a sleep problem. Symptoms are present during the day and patients may not associate EDS with night time disturbances. Moreover, patients often consider EDS equivalent to physical fatigue, which is in fact a different symptom. Conversely, some patients merely complain of being "fatigued" to their doctor, whereas in fact they intend to say that they have EDS. Clearly, this requires careful and proactive history taking by the physician or Parkinson nurse specialist.

### How to recognize sleep problems in PD patients?

Previous studies have shown that presence of sleep disorders influences quality of life in PD patients.[1–3] Therefore we should prevent under–recognition and under–treatment of this problem. In both **Chapter 2.1** and **Chapter 2.2** we offer practical tools which could help in the detection and diagnosis of sleep problems. In **Chapter 2.2** we showed that using a priority list can help highlighting the presence of important sleep issues to discuss during the consultation. In **Chapter 2.1** we recommend a useful chart which separates the possible sleep disorders present and classifies them in four major categories: daytime sleepiness, nocturnal motor symptoms, sleep–related breathing disorders and disorders of insomnia. In just a few minutes, using a set of recommended questions, the treating neurologist can identify if a patient is suspected of having any of the sleep disorders. Second, we provide a list pointing out which additional information is necessary to make a final diagnosis and to decide whether or not referral to a sleep center is needed.

One could argue in favor of sending every PD patient to a specialist sleep center at least once, to prevent the under–recognition and undertreatment of sleep problems. Especially since **Chapter 2.2** shows the importance of sleep to the PD patient.

A diagnostic flow chart can facilitate the early detection of sleep disturbances in PD.

A priority list can be used to prioritize patient centered quality of life issues and detect sleep problems in PD patients.

Every PD patient deserves to see a sleep medicine specialist at least once.





## Impaired bed mobility in Parkinson's disease

Although important for many PD patients, the subject of impaired bed mobility (IBM) and sleep problems have so far received little attention in research. In **Chapter 3.1** we showed a clear detrimental influence of difficulties turning around in bed on the quality of nocturnal sleep. We studied a large cohort of 240 PD patients, focusing specifically on the relation between sleep quality on one hand, and the presence and frequency of impaired bed mobility on the other. Impaired bed mobility was present in 56.3% of patients. The prevalence of poor sleep was higher in patients with impaired bed mobility, as reflected by significantly higher mean PSQI scores (PD+IBM 7.7±4.1 vs.PD–IBM 6.1±3.4, p = .001). When we corrected the results for age, disease duration, H&Y stage and LED, presence of impaired bed mobility still had a significant effect on PSQI total score (R–squared = 0.066, standardized–beta = 0.163, p=0.026). The relation between the frequency of difficulties turning around in bed and sleep quality showed a linear trend (contrast estimate 1.9, p=0.001).

We studied the influence of impaired bed mobility on objective sleep parameters in **Chapter 3.2.** We compared the influence of subjective impaired bed mobility on objective sleep quality in patients with PD. We found that PD patients who complain of subjective impaired bed mobility had a significantly diminished sleep efficiency (PD+IBM 63.5% (26.2–85.6) vs. PD–IBM 78.4% (54.8–92.6), p<.001) and a shorter total sleep time compared to patients without complaints (PD+IBD 298.0 min (103.0–419.0) vs. PD–IBM 379.6 min (243.0–530.0), p = .001).

### Impaired bed mobility and sleep quality

Although in clinical practice impaired bed mobility is considered to play an important role in diminished sleep quality in PD patients, the subject has received little attention in research so far. Findings by van Hilten et al. suggest a link between sleep maintenance problems and problems turning around in bed, as the results showed a higher frequency of problems turning around in bed in PD patients compared to controls. This was only the case for PD patients and controls with sleep maintenance problems, but not patients with sleep initiations problems.[4] These results, however, could also be explained by the co–occurrence of both insomnia and impaired bed mobility in PD, without a causal relation. Gjerstad et al. found that problems turning around in bed increased with the duration of PD over a study period of eight years.[5] During this period the prevalence of insomnia did not increase, which suggests that there is no correlation between both entities. Stack et al. studied recumbent turning strategies in 39 PD patients, seven of whom were completely unable to turn in

bed.[6] They found that sleep initiation and maintenance problems were comparable between both groups. A major problem of these studies is that PD patients were compared with healthy controls. Research has however showed that sleep quality is different in both groups. Therefore the studies do not actually imply whether sleep quality is diminished by the presence of impaired bed mobility or if other factors, such as the PD itself, are influencing sleep. Our studies were the first to find an association between sleep disruption and impaired bed mobility within a group of PD patients. We showed that both subjective sleep quality measured with questionnaires as well as objective sleep quality based on PSG findings are worse in PD patients with complaints of impaired bed mobility.

## Body position changes in PD

In **Chapter 3.2** we also objectified the complaint of impaired bed mobility. We compared actual body position changes between 24 PD patients with and 20 without complaints of impaired bed mobility and 44 healthy controls. Our results showed only a marginally significant difference between turns during the total night (PD 7.6/h (0.0–19.1) vs. controls 8.8/h (2.0–47.6), p = .046). Furthermore, no significant difference was found in number of turns between PD patients with and without complaints of impaired bed mobility (PD+IBM 6.6/h (0.3–15.0) vs. PD–IBM 8.1/h (0.0–19.1), p = .099). When focusing on actual body position changes during sleep alone the results did show a reduced frequency in patients with impaired bed mobility (PD+IBM 0.4/h (0.0–1.8) vs. PD–IBM 1.4/h (0.0–4.6), p=.015). There was a broad range in the frequency of body position changes however, and even subjects with almost no shifts did not necessarily have impaired sleep quality. More importantly, no correlation was found between turns during sleep and sleep efficiency (PD+IBM R squared = 0.043, p = .900).

A limited number of studies has focused on nocturnal activity in PD patients during sleep. Two studies reported increased nocturnal activity levels comparing PD patients to controls.[7,8] This probably does not directly imply that PD patients have higher activity during sleep. More likely this is caused by increased sleep fragmentation leading to more wake states during the night. We did not find any difference in activity level between PD+IBM and PD–IBM as measured with actigraphy. The controls, however, did not have actigraphy, so a comparison between PD and controls could not be made. One previous study focused on actual body position changes during sleep in PD. Laihinen et al. compared bed mobility in nine PD patients and 11 neurological healthy controls, using a static charge sensitive bed.[9] Movements were distributed over duration classes of < 5 sec, 5–10 sec, 11–15 sec, >15 sec. The results





showed that overall, PD patients had fewer movements and turning events were almost 20 sec longer in PD patients. Our results did not show a difference between body position changes per hour in PD patients compared to controls. We did find a reduced number of body position changes during sleep between PD+IBM and PD–IBM. Remarkably, this difference was only present during sleep and not during wake time. This is in contrast to what could be expected since PD patients complain of having impaired bed mobility when lying awake. No relation between sleep efficiency and impaired bed mobility could be found, suggesting that the insomnia is influenced by the subjective feeling rather than the actual body position changes.

The precise mechanism of impaired bed mobility is not clear. Problems turning in bed are probably a part of the overall axial motor impairments in PD. Rigidity as well as bradykinesia are considered to play a role. Steiger et al. found an association between difficulty turning in bed and both axial rigidity and whole body bradykinesia in 19 PD patients.[10] After levodopa treatment the turning in bed improved as well as the axial rigidity and bradykinesia. This however is in contrast to the findings of Lakke et al. describing patients with turning difficulties when lying recumbent.[11] Levodopa therapy improved rigidity and bradykinesia, but turning difficulties remained. The authors stated that these turning problems were probably caused by “axial apraxia” rather than rigidity or bradykinesia in these patients. Our results show that there is a group of patients with a small number of body position changes during the night, but without subjective complaints. To get more insight into the mechanism of impaired bed mobility this particular group should be studied further.

Nocturnal body movements and their influence should be studied in more detail in both the general population and PD patients in particular. Actigraphy does not seem to be the best method to register body movements, since activity levels do not give any information about speed, direction or patterns of a movement. Rather than actigraphy more advanced tools should be used, that register actual movement during sleep. As such one could think of video monitoring and analysis to observe body position changes during the night. Also body mobility measured with a compression sensor in the bed could be an option. When using accelerometers, more advanced devices using tri–axial accelerometers should be used. Also the best registration side is discussable; the best results are probably established by using a combination of sensors on the trunk as well as the extremities. A correlation between movements and sleep quality can be made preferably with objective measurement techniques such as PSG.

Previous studies on Parkinson medication show improvement on subjective bed mobility when using the administered drugs.[12,13] However, since our results show no actual differences in nocturnal movement in PD+IBM en PD–IBM, the exact physiology of this improvement is unclear. Does the medication lead to an actual improvement of bed mobility, or are improvements more subjective because of a sedative effect. A more multidisciplinary approach to bed mobility also suggests an improvement of sleep when using physiotherapeutic turning strategies in bed. Especially the Dutch guideline, but also the recent European guideline partly focus on improvement of bed mobility.[14] The expert opinion of physiotherapist in the field of PD describes an subjective improvement of sleep quality when using these strategies. More research is needed to clarify this problem, preferably comparing medication with physiotherapy. The use of video registration or tri–axialaccelerometry focusing on the turning strategies could be useful to get more insight into this problem.

Subjectively impaired bed mobility is negatively associated with both subjective and objective quality of nocturnal sleep. Whether or not this reflects a true causal relationship or a mere association requires further study.

PD patients with complaints of impaired bed mobility move less during sleep compared to PD without complaints, but not when lying awake at night.

Sleep seems to be disrupted by the subjective feeling of impaired bed mobility rather than actual diminished body position changes.

Activity levels between PD with and without impaired bed mobility are not different.





## Nocturnal movements in the preclinical phase of Parkinson's disease

Although previous studies suggested differences in nocturnal mobility between PD patients and controls, the study of **Chapter3.2** did not show increased activity levels during the night in PD patients, and also no decreased frequency of nocturnal turns. Body position changes during the night may, however, have different patterns compared to controls. These changes may also precede the onset of PD and could therefore be interesting to study as an early PD marker. In **Chapter 4** we compared nocturnal movements in 11 PD patients and 13 healthy controls and 33 non–PD individuals with a potential high risk for future development of the disease (HR–PD). All patients were investigated within the framework of the PMPP study (Progression Markers in the Premotor Phase of Parkinson's Disease).[15,16] In brief, individuals defined as HR–PD had hyperechogenicity of the substantia nigra in addition to concomitant risk or prodromal markers of PD. These subjects had at least one symptom defined as either (a) or (b): (a) one PD cardinal motor sign assessed by the Unified Parkinson's Disease Rating Scale (UPDRS–III) motor part, (b) two of the following prodromal/risk markers: prevalence of depression or history of depression, hyposmia, one–sided reduced arm swing, positive family history of PD.[17–19] All controls had normal echogenicity of the substantia nigra, no signs of acute psychiatric diseases and a negative family history of PD.[19,20] The results show that with respect to general movement assessment, mean acceleration was lower in PD patients compared to controls. Again the frequency of axial turns did not significantly differ between both groups, but the distribution and pattern of the axial turns did: total size of axial turns was smaller (PD 32.6° (17.5–46.9) vs. controls 46.72° (22.7–73.9), $p < .001$) and duration of turns was shorter (PD 5.7 s (4.1–8.8) vs. controls 6.96 s (5.6–10.2), $p = .001$) in PD patients. No differences were found between mean acceleration in HR–PD patients and controls. Furthermore, characteristics of axial turns were not different.

In agreement with the findings of **Chapter 3** no differences in frequency of nocturnal movements were found between PD patients and controls. Some aspects of nocturnal movements were different in PD patients however. In general, our data suggest that PD patients may attempt to turn, but are not able to reach the full size of these axial movements. Although size and duration of movements were altered in the PD group, the speed level of movements was similar to that of healthy controls. Previous studies on nocturnal movements are mentioned above, none of them focused on the pattern of movements we studied in **Chapter 4**, therefore a direct comparison with other studies cannot be made. From our findings, one could hypothesize that PD–related axial

motor dysfunction during the night influences the size of the movements rather than its speed. We can only speculate about the cause of these differences. Both rigidity as well as bradykinesia may contribute to these changes, as well as the difficulty that PD patients have in generating complex, sequential movements or axial synergies.[21,22] Future research should focus on this subject. Including more detail information on diurnal and nocturnal movements may lead to a more precise explanation, which can lead to more targeted therapy options. Based on questionnaires, sleep quality was not different between the three groups. In the study of **Chapter 4** we however did not include objective sleep measurements. Especially in the PD group it would be interesting to study the influence of the movement patterns changes on sleep structure.

Our second hypothesis stated that changes in nocturnal movement patterns might occur already in non-PD individuals with potential high risk for future development of the disease and may thus potentially serve as prodromal makers of the disease. We could not prove this hypothesis. We know, however, that nocturnal movements change somewhere in the course of progression of the clinically overt motor phase of PD. For example, rapid eye movement (REM) sleep behavior disorder (RBD) is a sleep disorder known to predict future onset of PD. After a period of 5 years around 28% to 45% of idiopathic RBD patients converted to PD and 40% to 65% after a period of 10 years.[23,24] Patients with RBD have overt movements during the normally, atonic REM phase of sleep. This suggests that RBD results in changed motor patterns in high risk individuals. Longitudinal assessment is necessary to further follow up these high risk individuals to study if changes precede the diagnosis of PD, and potentially serve as a high risk marker. However the mechanism of RBD is still not clear and movements during REM sleep could not be related to other movements in PD.

Not the frequency but the mean acceleration, size and duration of axial movements are altered in the overt motor phase of PD.

Nocturnal motor patterns in individuals who are at high risk for future development of PD are comparable with healthy controls.

Nocturnal motors patterns, as these can be analyzed currently, are not a useful biomarker for the early detection of PD.





## Actigraphy as a diagnostic tool in REM sleep behavior disorder

Assessing the presence of RBD in PD patients based on the clinical interview alone often results in misdiagnosis. According to the current diagnostic criteria, the diagnosis of RBD requires a clinical interview and video polysomnography (v-PSG).[25] In clinical practice, however, this is not always feasible, since it is time consuming and expensive. Therefore there is a need for less expensive, easy to use devices to diagnose RBD. In **Chapter 5** we studied the use of actigraphy as a diagnostic tool for RBD in PD patients. We studied 45 PD patients with and without the clinical diagnosis of RBD. The diagnosis was based on the clinical interview accompanied with v-PSG, according to the ISCD-II criteria. The main outcome measure was the total number of bouts classified as “wake”, compared between patients with (PD+RBD) and without (PD- RBD) RBD. The total number of wake bouts was significantly higher in RBD patients (PD+RBD 73.2±40.2 vs. PD-RBD 48.4±23.3, p = .016). A cut off of 95 wake bouts per night resulted in a specificity of 95.5%, a sensitivity of 20.1% and a positive predictive value of 85.7%. Based on the clinical interview, seven patients were suspected of having RBD, but they did not fulfill the full ICSD-II criteria. All but one of these patients had sleep initiation or sleep maintenance problems (insomnia); two were diagnosed with obstructive sleep apnea syndrome, two had restless legs syndrome, three showed an increased level of periodic leg movements, and one reported nocturnal hallucination. Six of the patients had a wake bout count lower 95.

Wake bouts as scored by actigraphy have been suggested before as a possibly useful outcome measure in the diagnostic workup of RBD in PD patients: our findings are in agreement with Naismith et al., who studied 22 patients during 14 consecutive nights with actigraphy.[26] A major difference between our study and that of Naismith et al. was the fact that the actual number of wake bouts was almost twice as high in our patient groups compared to theirs. Since the sensitivity setting of the devices the same, this could be caused by difference in epoch length settings, which was 0.25 min in our study, and 0.50 in the study of Naismith et al.[26] In addition, we used v-PSG in combination with a clinical interview by a sleep medicine specialist as the gold standard for the diagnosis of RBD, instead of questionnaires.

Our results show that using actigraphy, the number of bouts classified as “wake” is significantly higher in PD patient with RBD compared to PD patients without. Accordingly, we show that actigraphy has a high specificity and a good positive predictive value for diagnosing RBD in PD patients. In our study we also focused on the

use of actigraphy in clinical practice. Our results show that using an epoch length of 0.25 min and a cut–off of 95 wake bouts per night, actigraphy is a highly specific tool, albeit with a low sensitivity. Based on a semi–structured clinical interview alone, we found seven patients incorrectly suspected of having RBD. Of these, only one patients scored above the threshold of 95 wake bouts per night. Therefore, these results show an additional value of using actigraphy next to a clinical interview in the diagnostic trajectory of RBD to exclude its presence.

Contrary to the high specificity and low sensitivity of actigraphy, RBD questionnaires had a high sensitivity (96%) and a somewhat low specificity (56%).[27–30] Combining actigraphy and RBD questionnaires could therefore lead to a more accurate diagnosis of RBD. The combination of these two tools could reduce the need for v–PSG, which is more complex and less readily available. Future research should study if a combination of both methods could optimize the diagnosis of RBD in PD patients in clinical practice.

Measured with actigraphy, the number of bouts classified as wake is significantly higher in PD patients with RBD compared to PD patients without RBD.

A cut off of 95 wake bouts per night results in a specificity of 95.5%, a sensitivity of 20.1% and a positive predictive value of 85.7%.

Actigraphy has an additional value next to the clinical interview alone in the diagnostic trajectory of RBD in PD patients.





## Conclusions and future perspectives

Our studies show that sleep is an important issue for the patient with PD. Poor sleep quality is a reason to ask for medical attention. Problems turning around in bed resulting in impaired bed mobility have a negative influence on both subjective as well as objective sleep parameters. Interestingly, we could not find a correlation between body position changes and sleep efficiency during the night, suggesting the poor sleep quality is caused by the complaint of impaired bed mobility rather than the actual body position changes. Not frequency but speed and duration of axial nocturnal movements are altered in patient with PD. However when these changes appear during the disease process is not clear, they are not present yet in individuals with some minor complaints of PD. Actigraphy has an additional value to the clinical interview alone in the diagnostic trajectory of RBD in PD patients. More research on the role of body position changes on sleep quality in necessary in PD patients as well as in the healthy population. This will finally lead to better and more individualized treatment of sleep problems in PD patients.

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# Nederlandse samenvatting

## Ziekte van Parkinson

De ziekte van Parkinson is een progressieve hersenziekte die zich kenmerkt door problemen in het bewegen. De criteria om de diagnose te stellen bestaan uit vertraging van bewegingen (bradykinesie) in combinatie met stijfheid (rigiditeit), beven (tremor), of afwijkende houdingsreflexen. Naast de bewegingsproblemen zijn er ook andere symptomen die niet met bewegen te maken hebben aanwezig bij parkinsonpatiënten. Deze klachten hebben soms meer invloed op de kwaliteit van leven dan de bewegingsklachten. Hierbij kan gedacht worden aan problemen met de reuk, autonome functiestoornissen zoals obstipatie en urine–incontinentie, depressiviteit en slaapproblemen.

## Slaap

Slapen in belangrijk voor elk individu. Tijdens de slaap rust het lichaam uit en worden ervaring van de dag opgeslagen in het geheugen. Te weinig slaap of slechte slaapkwaliteit leidt tot problemen overdag zoals ongewild in slaap vallen, concentratie en geheugenproblemen. Slaap kan worden gemeten met polysomnografie (PSG), dit zijn metingen van een combinatie van hersenactiviteit (EEG), spieractiviteit (EMG), oogbewegingen (EOG) en cardiorespiratoire parameters.

Af en toe slecht slapen is niet ongebruikelijk, maar meerdere slechte nachten achter elkaar zouden kunnen passen bij een slaapstoornis. Slaap kan verstoord worden door externe factoren zoals geluid, stress en pijn, maar slaapstoornissen kunnen ook door pathofysiologische veranderingen worden veroorzaakt. Slaap wordt opgedeeld in problemen met in– of doorslapen (insomnie), slaap gerelateerde ademhalingsstoornissen (zoals slaap apneu), slaperigheid overdag (hypersomnie), slaapstoornissen die van invloed zijn op de biologische klok (circadiane ritme stoornissen), en abnormale bewegingen tijdens de slaap (parasomnieën en slaap gerelateerde bewegingsstoornissen).

## Slaapproblemen bij de ziekte van Parkinson

Circa 90% van de parkinsonpatiënten ervaart problemen met slapen. Gebleken is dat gestoorde slaap een belangrijke negatieve invloed heeft op kwaliteit van leven. Alle slaapstoornissen zoals boven beschreven kunnen voorkomen bij de ziekte van Parkinson. Daarnaast kunnen ook de bewegingsklachten van de ziekte van Parkinson de slaap verstoren. De tremor verdwijnt over het algemeen tijdens lichte slaap, maar wanneer hij heftig is kan hij de slaap verstoren. Veel parkinsonpatiënten geven aan dat ze moeite hebben met omdraaien in bed. Wat hier de precieze oorzaak van is, is nog niet precies duidelijk. Allereerst kan de vertraging in het bewegen een rol spelen, maar ook de stijfheid kan van belang zijn. Daarnaast kunnen pijnklachten en over beweeglijkheid de nacht verstoren. Eerdere studies hebben aangetoond dat slechte slaapkwaliteit geassocieerd wordt met moeite met omdraaien in bed. Of patiënten die aangeven moeite te hebben met omdraaien ook daadwerkelijk minder draaien 's nachts is echter niet bekend.

## Inhoud proefschrift

Hoewel slaapstoornissen veel voorkomen bij parkinsonpatiënten en een belangrijke negatieve invloed hebben op kwaliteit van leven, blijft het vaak een onderbelicht onderwerp in de spreekkamer van de neuroloog. Hierbij speelt de tijdsdruk een rol, waarbij in korte tijd meerdere facetten van de ziekte moeten worden besproken. Daarnaast hebben veel neurologen weinig ervaring met slaapstoornissen, waardoor ze niet precies weten wat er besproken dient te worden. **Hoofdstuk 2** geeft inzicht welke slaapproblemen spelen bij parkinsonpatiënten en wat het belang van deze problemen is voor de patiënten. Daarnaast leveren we verschillende handvatten om slaapproblemen te detecteren in de spreekkamer. **Hoofdstuk 2.1** bevat een gedetailleerde introductie over de laatste ontwikkelingen omtrent de herkenning en diagnostiek van slaapproblemen bij parkinsonpatiënten. Allereerst ontwikkelden we een stroomdiagram dat door iedere neuroloog gebruikt kan worden voor de herkenning van slaapstoornissen. Daarnaast geven we adviezen omtrent de verdere diagnostiek en geven we aan wanneer een patiënt verwezen dient te worden naar een slaapcentrum. In **hoofdstuk 2.2** gebruiken we een prioriteitenlijst om vast te stellen hoe belangrijk slaap is voor de parkinsonpatiënt zelf. Voor een consult bij de neuroloog werd patiënten gevraagd een top 5 te maken van problemen die zij graag zouden bespreken met de neuroloog. Van de 153 parkinsonpatiënten zette 37.9% slaap op de prioriteitenlijst, hiermee is het het 6e item op een lijst van in totaal 23 onderwerpen. 70% van de patiënten had een verstoorde slaap. Er was sprake van een significant slechtere slaapkwaliteit bij patiënten die slaap prioriteerden ten opzichte van patiënten die slaap niet in hun top 5 zetten. Niet alle patiënten met slaapproblemen zetten slaap op het lijstje. Het zou kunnen dat voor deze patiënten slaap op het moment van bezoek minder belangrijk was dan andere problemen. Opvallend is dat patiënten die slaperig zijn overdag, slaap niet vaker op het lijstje zetten dan patiënten die hier geen klachten van hadden. Dit komt mogelijk doordat ze slaperigheid overdag niet zien als een slaapprobleem.

Een stroomdiagram kan helpen bij de herkenning van slaapproblemen bij parkinsonpatiënten.

Een prioriteitenlijst kan gebruikt worden om verschillende problemen, waaronder slaapproblemen vanuit het patiënten perspectief te signaleren.

Elke parkinsonpatiënt met slaapklachten verdient een bezoek aan een slaapcentrum.

**Hoofdstuk 3** richt zich op bewegingsproblemen tijdens de nacht. In **hoofdstuk 3.1** beoordeelden we wat de invloed van moeite met omdraaien in bed is voor parkinsonpatiënten op de subjectieve slaapkwaliteit, gemeten met slaapvragenlijsten. We onderzochten 240 parkinsonpatiënten. 56.3% van de patiënten gaf aan moeite te hebben met omdraaien in bed. Slaapkwaliteit was significant slechter in de groep parkinsonpatiënten die aangaven problemen te hebben met omdraaien in bed ten opzichte van parkinsonpatiënten zonder deze klacht. In **hoofdstuk 3.2** beoordelen we de invloed van moeite met omdraaien in bed op de objectieve slaapkwaliteit, gemeten met PSG. Daarnaast werd onderzocht of patiënten die aangeven moeite te hebben met omdraaien in bed ook daadwerkelijk minder positiewisselingen maken in de nacht. We vergeleken 44 parkinsonpatiënten met en zonder klachten. Verschillende slaapparameters werden geregistreerd middels PSG. Vergelijkbaar met onze bevindingen in **hoofdstuk 3.1** bleek dat de slaapkwaliteit significant slechter was en totale slaaptijd significant korter bij parkinsonpatiënten die aangaven moeite te hebben met omdraaien in bed. Van alle patiënten die deelnamen aan de

studie werd bepaald hoe vaak zij gedurende de nacht van houding veranderden. Weliswaar werd een kleine afname gevonden van het aantal houdingsveranderingen gedurende de slaap bij parkinsonpatiënten met klachten, echter gedurende de gehele nacht, dus slaap en waak perioden, werd geen significant verschil gevonden. Dit is opmerkelijk, zeker omdat patiënten voornamelijk klagen over de perioden waarin zij wakker liggen. Tevens werd geen correlatie gevonden tussen slaapkwaliteit en aantal houdingsveranderingen gedurende de nacht. Mogelijk dat de klacht dus een belangrijkere invloed heeft op de slaapkwaliteit dan het aantal houdingsveranderingen zelf.

Klachten over moeite met omdraaien in bed bij parkinsonpatiënten zijn geassocieerd met zowel subjectieve als objectieve afname van slaapkwaliteit.

Parkinsonpatiënten met klachten van omdraaien in bed, hebben minder houdingsveranderingen tijdens hun slaap, maar niet tijdens waak of over de gehele nacht.

Slaap lijkt eerder te worden verstoord door het subjectieve gevoel dat omdraaien in bed moeilijk gaat, dan door het daadwerkelijke aantal houdingsveranderingen tijdens de nacht.

**Hoofdstuk 4** gaat in op nachtelijke bewegingen in de periode voordat de motore klachten van de ziekte van Parkinson aanwezig zijn. Omdat eerdere studies geen duidelijk verschil vonden tussen de frequentie van houdingsveranderingen tijdens de nacht bij parkinsonpatiënten en gezonde controles, onderzochten we allereerst of andere facetten van bewegen 's nachts zoals de grootte, duur en snelheid van de beweging wel verschillend zijn tussen beide groepen. Daarnaast onderzochten we of deze veranderingen reeds aanwezig zijn bij personen met een hoog risico op het krijgen van de ziekte van Parkinson. We vergeleken de nachtelijke bewegingen van 11 parkinsonpatiënten, 13 gezonde controles en 33 personen zonder de ziekte van Parkinson, echter met een hoog risico op het ontwikkelen van de ziekte (zoals reeds afgenomen armzwaai, reukproblemen, afwijkingen van de hersenstam op echo). Bij de vergelijking tussen parkinsonpatiënten en gezonde controles vonden





we dat parkinsonpatiënten kleinere draaien maakten en de draaien korter duurden. De frequentie van het aantal bewegingen en de snelheid was niet veranderd. Om de tweede hypothese te toetsen vergeleken we de personen met een hoog risico met gezonde controles. Hierbij werden geen verschillen gevonden in de verschillende facetten van de beweging. Mogelijk dat deze in een later stadium ontstaan.

Parkinsonpatiënten maken niet minder draaien in de nacht, maar de houdingsveranderingen zijn wel kleiner en duren minder lang ten opzichte van gezonde controles.

Nachtelijke bewegingspatronen bij personen met een hoog risico op het ontwikkelen van de ziekte van Parkinson zijn vergelijkbaar met gezonde controles, en lijken daarmee geen duidelijk indicator voor het ontwikkelen van de ziekte.

Tot slot bestudeerden we een andere veel voorkomende nachtelijk bewegingsstoornis bij de ziekte van Parkinson in **hoofdstuk 5**. Rapid eyemovement (REM) sleep behavior disorder (RBD) is een slaapstoornis die zich uit in bewegingen tijdens de nacht. Deze bewegingen, treden op tijdens de REM-slaap, die normaal gekenmerkt wordt door afwezigheid van spierspanning. Tijdens de REM slaap droomt een persoon gewoonlijk. Bij patiënten met RBD lijkt het dan ook vaak of zij op het moment van onrust hun droom aan het uitvoeren zijn. Vaak zijn deze dromen agressief of beangstigend van karakter. Patiënten maken dan ook vaak slaande of schoppende bewegingen. Uit eerdere onderzoeken is gebleken dat personen met RBD later zeer vaak de ziekte van Parkinson ontwikkelen. Andersom komt RBD voor bij ca 50% van de parkinsonpatiënten. Om de diagnose te kunnen stellen is volgens de criteria een duidelijke anamnese het liefst door een slaapdeskundige geïndiceerd, daarnaast moet een PSG worden verricht. Dit is echter tijds- en kosten invasief. Er wordt dan ook gezocht naar goedkopere en makkelijkere middelen om de diagnose te stellen. In het verleden is geopperd om actometers (bewegingsmeters) te gebruiken. Een eerdere studie toonde een significante toename van waakperioden bij parkinsonpatiënten met RBD, vergeleken met parkinsonpatiënten zonder RBD. Wij hebben deze studie herhaald met een grotere groep patiënten en hebben daarnaast gekeken naar een mogelijke afkapwaarde om de patiënten met en zonder RBD in de

klisniche praktijk te kunnen onderscheiden. We onderzochten 45 parkinsonpatienten en beoordeelden op basis van de officiële criteria of er sprake was van een RBD. Alle patiënten kregen hiervoor een PSG, daarnaast kregen ze 8 nachten een actometer om, waarvan de eerste nacht gesynchroniseerd werd met de slaaptijden van de PSG. Conform het andere onderzoek vonden wij een significante verhoging van het aantal waakperioden bij patiënten met RBD. Een afkapwaarde van 95 waakperioden resulteerde in een specificiteit van 95.5%, een sensitiviteit van 20.1% en een positief voorspellende waarde van 85.7%. Wanneer bij de onderzochte patiënten alleen werd uitgegaan van de anamnese werden 7 patiënten onterecht verdacht voor RBD. Hiervan hadden er 6 minder dan 95 waakperioden. Dit suggereert dat het gebruik van een actometer bij deze patiënten zinvol zou kunnen zijn. Bij eerdere onderzoeken over vragenlijsten in het diagnostisch traject van RBD is gevonden dat zij een hoge sensitiviteit hebben en een lagere specificiteit. Mogelijk dat een combinatie van vragenlijsten en actometers een waardevolle methode zou zijn voor het diagnosticeren van RBD.

Het gebruik van een actometer toont een hoger aantal waakperioden bij parkinsonpatiënten met RBD dan in parkinsonpatiënten zonder RBD.

Een afkapwaarde van 95 waakperioden leidt tot een specificiteit van 95.5%, een sensitiviteit van 20.1% en een positief voorspellende waarde van 85.7%.

Een actometer heeft een toegevoegde waarde naast de anamnese in het diagnostisch proces van RBD bij parkinsonpatiënten.

# Dankwoord

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# Curriculum vitae

# Curriculum Vitae

Maartje Louter was born on December 7th 1981 in Amsterdam. After finishing secondary school in 2000 at the Murmellius gymnasium in Alkmaar, she studied Medicine at the Radboud University Nijmegen. She obtained her doctoral degree in 2007. During her study she was very active in the student's rowing club N.S.R.V. Phocas. She attended the board as secretary and equipment commissioner in 2002–2003. From 2009–2013 she was a member of the board and later the president of the reunion association of the N.S.R.V. Phocas. After her study she worked as a resident on the department of neurology of St Antonius ziekenhuis in Nieuwegein and Utrecht. In 2009 she started her PhD project on sleep disorders in Parkinson's disease under supervision of prof. dr. B.R. Bloem, prof. dr. D.A.A.P. Pevernagie, dr. S. Overeem and prof dr. J.B.A.M. Arends. During this period she attended the 3 year European program for young, promising researchers in the field of sleep medicine, including an internship in the sleep laboratory of prof. Plazzi in Bologna, Italy. Furthermore she gave different lectures for neurologists and patients on the subject of sleep disorders in Parkinson's disease. In 2013 she started working as a resident on the department of neurology at Medisch Centrum Haaglanden in Den Haag, where she started her training in January 2014. Maartje lives in Utrecht and is married to Bart. On June 10th 2014, their son Tijn was born.

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